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(54) Title: HYDROPHILIC, HYDROPHOBIC, AND THERMOREVERSIBLE SACCHARIDE GELS AND FOAMS, AND METHODS FOR PRODUCING SAME

(57) Abstract

Polymerizable saccharide monomers are made by the reaction of a saccharose and a (meth)acrylate. Hydrophilic, hydrophobic and thermoreversible gels and foams are formed upon polymerization of the saccharide monomers. Hydrophilic sucrose monomers are synthesized by reaction of sucrose with an epoxy acrylate. Hydrophobic sucrose monomers are synthesized by reaction of sucrose with methacrylol chloride followed by acetyl chloride. Thermoreversible sucrose monomers are obtained by modifying sucrose with polymerizable substituents prepared from methacryloyl chloride and aminocarboxylic acids. The modified sucrose monomers are copolymerized with hydrophobic poly(alkyleneoxide) (meth)acrylates to produce hydrogels exhibiting inverse thermoreversible properties. The thermosensitive hydrogels are biodegradable and can be used in the area of controlled drug delivery.

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HYDROPHILIC, HYDROPHOBIC, AND THERMOREVERSIBLE SACCHARIDE GELS AND FOAMS, AND METHODS FOR PRODUCING SAME

Technical Field

The present invention relates to gels and foams derived from saccharides. The invention particularly relates to polymerizable derivatives of saccharides,
5   e.g., sucrose. The gels and foams can be used in the controlled release of drugs.

Background of the Invention

Saccharides are ubiquitously present in plants and some are quite inexpensive. Even highly purified sucrose
10   can be obtained at low cost. All of the hydroxyl groups of a saccharide molecule can be chemically modified, e.g., the eight hydroxyl groups of sucrose. The degree of modification can be controlled, for instance, by changing the reaction ratio. These considerations have
15   led to extensive research on the chemistry of the saccharides, particularly the least expensive ones.

For example, the research literature reveals that sucrose has been used to build polymer networks [Gruber, H. (1981); Patil, D., et al., (1991); Garcia-Gonzalez, et
20   al., (1993)]. Glycidyl (meth)acrylates have been used to modify polysaccharides, such as starch [Lepisto, M., et al. (1983);
Laakso, T., et al., (1987); Artursson, P., et al. (1984)] and dextran [Edman, P., et al. (1980); Smedt, S.C.D., et
25   al. (1995)]. Also, the formation of swellable hydrogels from proteins, such as albumin, has been described [Park,

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K., (1988); Shalaby, W.S.W., et al. (1990)]. Polymer hydrogels and microspheres have been made by these approaches.

Hydrophilic gels have been prepared from sucrose, for example, by polymerization of a sucrose ester. Thus, polymerization of a sucrose acrylate monomer has been described [Strumia, M.C., et al. (1991)]. Further, linear polyesters of sucrose have been described [Patil et al., (1991)]. These latter sucrose linear polyesters were produced using an enzyme system.

Although extensive research has been performed on hydrogels, little research is related to hydrogel foams. When the hydrogel foams are formed, the polymer chains are separated by empty spaces. Thus, water can be absorbed into the foams by capillary reaction. Furthermore, the porous structure affords foams having hundreds of times more surface area and shorter diffusion distance than hydrogels, making the swelling rate of foams hundreds of times faster than that of hydrogels. The fast swelling ability is important, for instance, in designing controlled release drug delivery systems, especially oral dosage forms [Shalaby, W.S.W., et al. (1992)].

Additionally, environment-sensitive hydrogels have been studied extensively. Hydrogels having the ability to respond to changes in environmental factors such as pH, temperature, electric field, or light can find application in drug delivery, biotechnology, biosensors, and semiconductors. Moreover, hydrogels that can respond to stimuli caused by particular diseases may provide a basis for developing new smart drug delivery systems. For example, attempts have been made to develop hydrogel systems that respond to pH changes and specific ligands in delivering insulin, however, they are unsatisfactory. [Jeong, S.Y., et al., (1984); Horbett, T.A., et al. (1984)].

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Thermoreversible hydrogels have been proposed for use in a new drug delivery system as well as a bioseparation system [Yoshida, R., et al., (1993); Hoffman, A.S., et al., (1986); Dong, L.C., et al., (1986)]. Various applications for thermoreversible hydrogel systems have been proposed by researchers [Shalaby, S. W. (1991)].

Thermoreversible hydrogels prepared by the copolymerization of N-isopropyl acrylamide and methacrylic acid, lightly crosslinked with N,N-methylene-bisacrylamide have been studied [Hoffman, A.S., et al., (1986); Dong, L.C., et al., (1986)]. Copolymer hydrogels of N-isopropyl acrylamide and butyl methacrylate reportedly exhibited thermoreversible changes in volume with temperature [Bae, Y.H., et al., (1988)]. Also, hydrogels containing N-methacryloyl α-amino acid esters and 2-hydroxypropyl methacrylate, which were crosslinked with polyethylene glycol (600) dimethacrylate, were reported to show temperature-dependent reversible volume changes [Yoshida, M., et al., (1989)]. Hydrogels synthesized from methacryloyl dipeptides have also been characterized [Yoshida, M., et al., (1991)]. In addition, an interpenetrating polymer network of N-acryloyl pyrrolidone and poly(oxyethylene) has been described [Bae, Y.H., et al. (1987)].

In the patent art, U.S. Patent No. 3,103,508 discloses polymerizable esters formed from sugars and α,β-unsaturated polymerizable acids.

U.S. Patent No. 3,215,137 discloses an immobilizing bandage which employs a sucrose ester, the viscosity of which may be reduced by adition of a polyethylene glycol dimethacrylate.

U.S. Patent No. 3,225,012 discloses nylon-type polyamides derived from carbohydrates.

U.S. Patent No. 3,356,652 discloses vinyl derivatives of tetra-acetylated glucose.

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U.S. Patent No. 4,042,538 discloses vinylbenzoyl esters of mono- and disaccharides, which can be copolymerized with styrene or methacrylates.

U.S. Patent No. 4,663,388 discloses a "coupling agent", which comprises a saccharide having a pendant ethylenically unsaturated group, such as an acrylamide moiety.

U.S. Patent No. 5,164,492 relates to approaches to forming polymers having saccharide residues at their sidechains.

U.S. Patent No. 5,116,961 discloses the formation of a trimethacryloyl sucrose having methylated hydroxyl groups. U.S. Patent No. 5,248,747, which is a continuation-in-part of U.S. Patent No. 5,116,961, relates to polymers formed using the trimethacryloyl sucrose as a cross-linking agent.

Desired are novel saccharide monomers that can be polymerized to form biodegradable gels and foams. Such gels and foams should be more environmentally friendly than purely synthetic gels and foams, and may be imparted with physical and chemical properties conducive to their use in medical and veterinary applications.

Summary of the Invention

The present invention is for novel unsaturated saccharide compounds that are polymerizable to form gels and foams. These saccharide compounds are represented hereinbelow by formulas (I-VII) as follows:

$$S \left(O \underset{OH}{\longrightarrow} O \underset{R}{\overset{O}{\longrightarrow}} \right)_n \qquad (I)$$

$$\left(R' \overset{O}{\longrightarrow} O \right)_m S \left(O \underset{R}{\overset{O}{\longrightarrow}} \right)_n \qquad (II)$$

(III)

(IV)

(V)

(VI)

(VII)
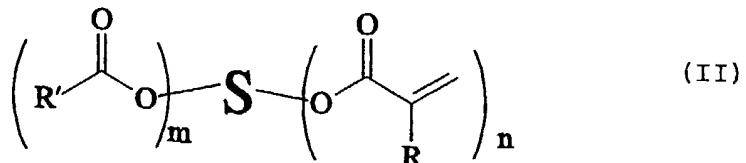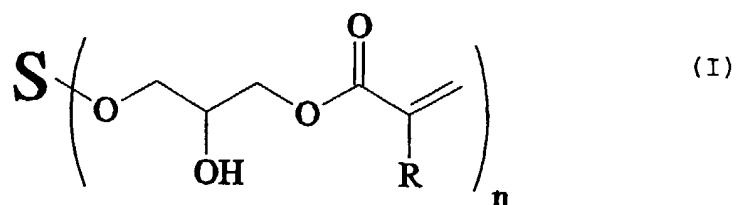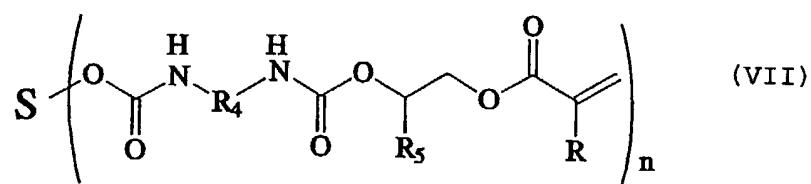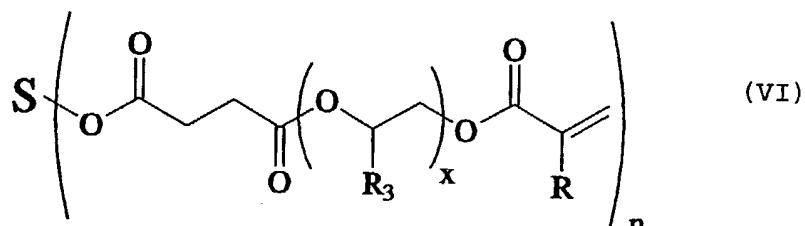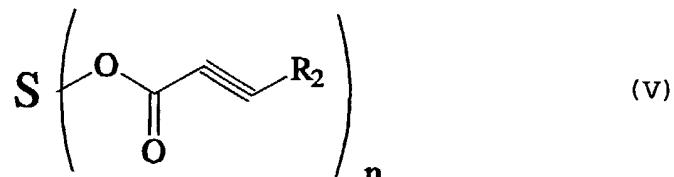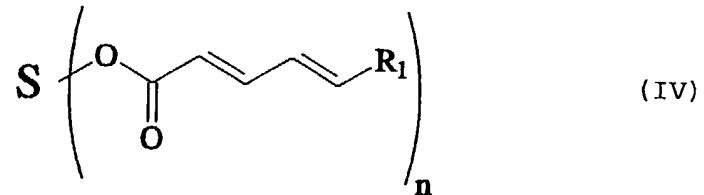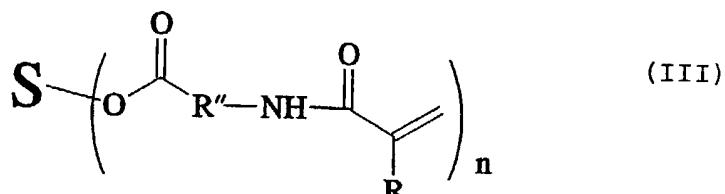
In each of the above formulas, S represents a
saccharide residue, R is hydrogen or a lower alkyl group,
e.g., methyl, and n is an integer from 1 to 8. In
formula (II), R' represents an alkyl, aryl or alkaryl
group, and m is an integer from 0 to 7. In formula
(III), R" represents an alkylene, arylene or alkarylene
diradical. In formula (IV), R_1 represents a lower alkyl
group. In formula (V), R_2 represents a lower alkyl
group. In formula (VI), R_3 is hydrogen or methyl, and x
is an integer from 1 to 10,000. In formula (VII), R_4

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represents a diradical, which can be an alkylene chain, and aromatic group, or an alkaryl group, and R_5 represents hydrogen or a lower alkyl group.

A hydrophilic saccharide gel is formed by polymerizing a saccharide monomer having formula (I) above. A hydrophobic gel is formed by polymerizing a saccharide monomer having formula (II) above. A gel having inverse thermoreversible properties is formed by copolymerizing a saccharide monomer having formula (III) above with a poly(alkyleneoxide) (meth)acrylate monomer, as defined herein, with or without a crosslinking agent.

Polymerization of a saccharide monomer having formula (IV) or (V) above produces a hydrophobic saccharide gel. Whenever a saccharide monomer having formula (VI) or (VII) is polymerized, a hydrophilic gel is produced.

Foams can also be produced by polymerizing a saccharide monomer shown above in formulas (I-VII), in the presence of a blowing agent. Particularly preferred are foams that have been dehydrated with an organic solvent, such as ethanol or acetone. Such foams have hydrophilic, hydrophobic or inverse thermoreversible properties, respectively.

Preferred saccharides include mono-, di-, tri- and higher oligosaccharides. More preferably a disaccharide is employed, most preferably, sucrose.

Associated methods of forming the instant saccharide monomers and polymers from a saccharide and corresponding (meth)acrylate are contemplated.

Brief Description of the Drawings

Fig. 1 illustrates chemical reactions that are the subject of the present invention, wherein S represents a saccharose.

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Fig. 2 shows the Thq (time to half equilibrium) measured for the swelling kinetics of hydrogels and foams.

Fig. 3 shows the swelling kinetics of S-2.5d gels in DDW (Δ), 0.9% NaCl solution (◊), and in 0.03 M HCl solution (□).

Fig. 4 illustrates the kinetics of various processes: Curve A-B-C describes the polymerization kinetic; A-B indicates the slow polymerization process in the absence of $NaHCO_3$; B-C represents the fast polymerization after the addition of $NaHCO_3$; the plateau after C shows the polymerization is completed; curve D-E-F describes the foaming curve with $NaHCO_3$ being added at point D; D-E is the foam rising phase; E-F represents the foam stabilizing phase; after point F, foam subsides rapidly.

Fig. 5 illustrates the degradation kinetics of S-2.5d gel (□) and foam (◊) in pH 12.5 NaOH solution at 37°C. It took 260 hours to degrade the gel but only 66 hours for the foam.

Fig. 6 depicts the degradation mechanism study of S-L using TLC. (A) sucrose; (B) degradation products of sucrose in acid; (C) degradation product of sucrose in base; (D) S-L monomer; (E) degradation products of S-L foam in acid; (F) degradation product of S-L foam in base.

Fig. 7 illustrates the structures of monomers used in the preparation of thermoreversible sucrogels of the present invention.

Fig. 8 depicts the thermosensitive volume change of sucrogels made of MACS and PPGM. The gels were cross linked with DMACS. The molar ratios of MACS:PPGM were 2:4 (●), 2:3 (O), and 2:2 (□).

Fig. 9 depicts the effect of crosslinking agent (DMACS) on the thermosensitive volume change of hydrogels made of MACS and PPGM. The molar ratios of MACS:PPGM was

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2:3. The concentrations of DMACS were 0.5 mole% (□) and 5.0 mole% (O).

Fig. 10 depicts the thermosensitive changes in volume of hydrogels made of PEGEEM only (O) and MACS-PEGEEM copolymers (□). The molar ratio of MACS-PEGEEM was 1:1 and the sucrogels were formed using DMACS as a crosslinking agent.

Fig. 11 depicts the thermosensitive changes in volume of hydrogels made of PPGM only (●), MLS-PPGM (□), and MLS-PEGEEM (O) copolymers. The molar ratios of MLS-PPGM were 1:1 and 2:1 (■) and that of MLS-PEGEEM was 1:1. The sucrogels were formed using DMACS as a crosslinking agent.

Fig. 12 depicts the thermoreversible swelling and shrinking of sucrogels; (A), sucrogels were made of MACS-PPGM copolymer with the molar ratio of 2:3 and the concentration of DMAC was either 0.5 mole% (O) or 5.0 mole% (●); (B), MACS-PEGEEM (O) and MAUS-PEGEEM (●) sucrogels with the molar ratio of 1:1; (C), MLS-PPGM (O) and MLS-PEGEEM (●) sucrogels with the molar ratio of 1:1. DMACS was used as a crosslinking agent.

Fig. 13 depicts the degradation of sucrogels; (A), in basic solution (pH 12.0); (B), in acidic solution (pH 2.0). The sucrogels were made of MACS-PPGM (●) and MLS-PPGM (O) copolymers. The molar ratio of monomers was 1:1 and the sucrogels were formed using DMACS as a crosslinking agent.

Detailed Description of the Invention

A vinyl-type (or acetylenic-type) saccharide monomer of the present invention is representd by formulas (I-VII) hereinbelow:

(I)

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(II)

(III)

(IV)

(V)

(VI)

(VII)
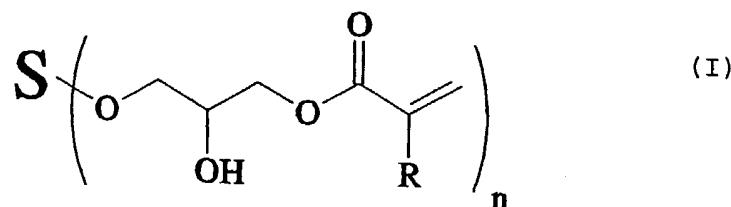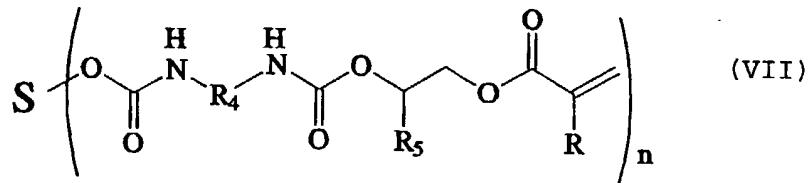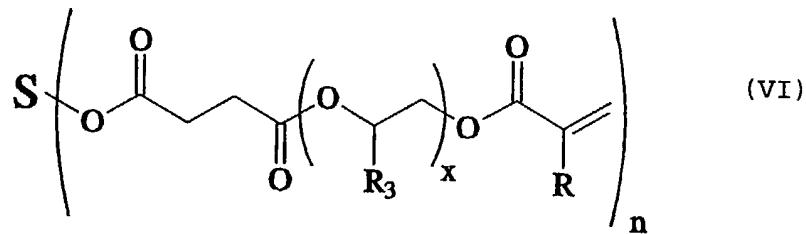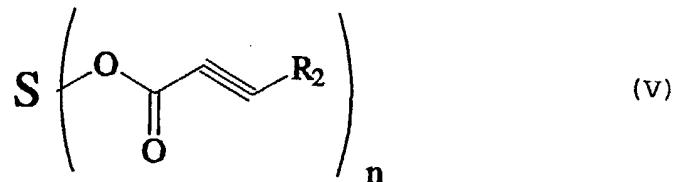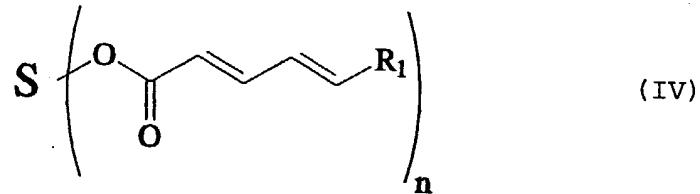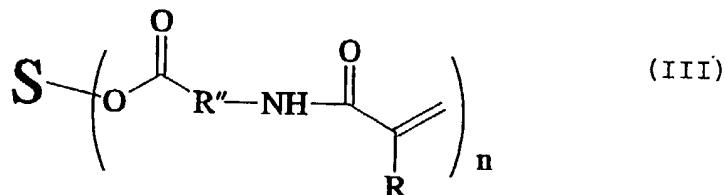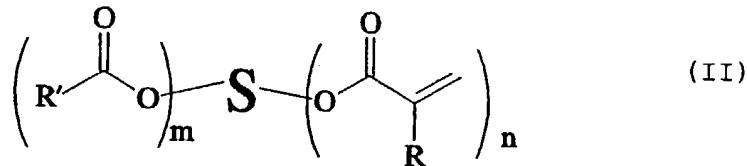
In formulas (I-VII), S represents a saccharide residue. The R group in each of the formulas can be hydrogen or a lower alkyl group. A preferred lower alkyl group is methyl. Accordingly, a (meth)acrylate moiety is preferred. In formulas (I-VII), n is an integer from 1

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to 8, and represents the extent of modification of the saccharide residue, e.g., with a (meth)acrylate group.

In formula (II), m is an integer from 0 to 7, and represents the extent to which the saccharide residue is modified with a hydrophobic group. The R' group in formula (II) can be an alkyl group, an aryl group, or an alkaryl group. When R' is an alkyl group, it is most preferably a lower alkyl group, e.g., methyl. A preferred aryl group is phenyl. A preferred alkaryl group is benzyl.

In formula (III), the R" group is an alkylene, arylene, or alkarylene diradical. Preferably, R" is a straight or branched chain alkylene group. For example, the R" group in formula (III) can be a methylene chain having the formula $(CH_2)_p$, where p represents the repeat number of methylene units, and ranges from 1 to 40, preferably 1 to 20, most preferably 4 to 12.

In formula (IV), the terminal R_1 group is preferably a lower alkyl group. The conjugated diene structure of the monomer can be polymerized in the usual free radical manner, i.e., with one or both olefin groups being saturated upon polymerization. Alternatively, the diene can react with an olefin of another molecule in Diels-Alder fashion, with the remaining unreacted olefin group being polymerized.

The terminal R_2 group of formula (V) is preferably a lower alkyl group. The alkynyl functionality of the molecule can be polymerized in free radical fashion, either once to produce an alkenyl functionality, or twice to saturate the molecule.

In formula (VI), a repeating glycol group is present in the molecule and is an ethylene oxide or propylene oxide group, i.e., R_3 represents a hydrogen or methyl group. In the formula, x represents the repeat number of the glycol group, and is an integer from 1 to 10,000. Adjacent to the saccharose group of the molecule is an

opened-up succinic anhydride linkage, which couples the glycol-(meth)acrylate portion of the molecule to the saccharose.

In formula (VII), R_4 represents a hydrocarbon diradical, i.e., an alkylene chain, aromatic group, or alkaryl group. Preferred groups for R_4 are n-butenyl, n-hexenyl, and n-octenyl chains, and among arylene and aralkylene groups, a tolyl diradical is preferred. R_5 of the formula represents hydrogen or a lower alkyl group, e.g., methyl.

A hydrophilic saccharide gel is formed by polymerizing a saccharide monomer having formula (I) above. A hydrophobic gel is formed by polymerizing a saccharide monomer having formula (II) above. A gel having inverse thermoreversible properties is formed by copolymerizing a saccharide monomer having formula (III) above with a poly(alkyleneoxide)(meth)acrylate monomer, as defined herein, with or without a crosslinking agent.

Polymerization of a saccharide monomer having formula (IV) or (V) above produces a hydrophobic saccharide gel. Whenever a saccharide monomer having formula (VI) or (VII) is polymerized, a hydrophilic gel is produced.

Hydrophilic, hydrophobic and inverse thermoreversible foams can also be produced by polymerizing a saccharide monomer shown above in formulas (I-VII), respectively, in the presence of a blowing agent. Whenever such foams are dehydrated with an alcohol, e.g., ethanol, as described hereinbelow, particularly desirable properties can be obtained.

Also contemplated are methods of synthesizing the unsaturated saccharide monomers defined by formulas (I-VII) hereinabove. The reactions are illustrated in Fig. 1.

Thus, as shown in Fig. 1A, a method for forming a saccharide monomer defined by formula (I) entails

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reacting the saccharide with an epoxy (meth)acrylate, such as glycidyl (meth)acrylate.

As shown in Fig. 1B, a method of synthesizing an ethylenically-unsaturated saccharide monomer according to formula (II) comprises reacting a saccharose with a (meth)acrylohalide in the presence of a base to form a saccharide (meth)acrylate. The saccharide (meth)acrylate is then reacted with an acyl halide in the presence of a base to form the ethylenically-unsaturated saccharide monomer. The halide leaving group in both instances can be chloride or bromide. A preferred (meth)acrylohalide is methacrylochloride, and an exemplary acyl halide is acetyl chloride.

As shown in Fig. 1C, a method of forming an ethylenically-unsaturated saccharide monomer according to formula (III) comprises reacting a saccharose with a (meth)acryloyl aminocarboxylic acid. The (meth)acryloyl aminocarboxylic acid is represented by the following formula:

$$\underset{HO}{\overset{O}{\|}} \underset{}{\overset{}{C}} \; R''-NH-\underset{}{\overset{O}{\|}}\underset{}{\overset{}{C}}\underset{R}{\diagup\!\!\diagdown}$$
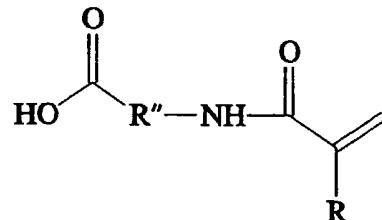
In the formula for the (meth)acryloyl aminocarboxylic acid, R represents hydrogen or a lower alkyl group and R" represents an alkylene, arylene, or alkarylene diradical, preferably a straight or branched chain alkylene group. Whenever the R" group in the formula is a simple methylene chain represented by the formula $(CH_2)_p$, p ranges from 1 to 40, preferably 1 to 20, and most preferably 4 to 12.

A reaction scheme for forming the (meth)acryloyl aminocarboxylic acid is depicted in Fig. 1C.

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Particularly preferred (meth)acryloyl aminocarboxylic
acids are N-methacryl-6-aminocaproic acid, N-methacryl-
leucine, and N-methacryl-11-aminoundecanoic acid, the
formulas of which appear in Fig. 7.

5   As shown in Fig. 1D, a method of forming the dienyl
saccharide of formula (IV) is depicted. Accordingly, a
2,4-dienyl carboxylic acid is reacted with hydroxyl
groups of the saccharide to form an ester linkage.
Similarly, as shown in Fig. 1E, the carboxyl group of an
10   α-alkynyl carboxylic acid is reacted with a saccharose to
produce an ester thereof. Standard esterification
reaction conditions can be employed.

        Fig. 1F depicts formation of a compound having
formula (VI). Thus, a (meth)acrylate of a poly(alkylene
15   oxide) is reacted with succinic anhydride in the presence
of base to open up the anhydride ring and couple the
molecule to the free alcohol group of the poly(alkylene
oxide). This activated (meth)acrylate compound is then
reacted with a saccharose under conventional conditions
20   to produce an ester linkage, as represented by formula
(VI).

        As shown in Fig. 1G, a saccharide-urethane compound
as represented by formula (VII) can be produced by
stoichiometrically reacting a (meth)acrylate having a
25   terminal hydroxyl group with a diisocyanate to give a
product having a single isocyanate moiety in the
molecule. This product is then coupled to the saccharose
via a urethane linkage to produce the target compound.
Both urethane forming reactions can be conducted under
30   standard conditions.

        Examples of the alkylene group represented by R" in
Fig. 1C and R_4 in Fig. 1G are straight chain or branched
chain alkylene groups having 1 to about 22 carbon atoms,
preferably about 1 to about 10 carbon atoms such as
35   methylene, ethylene, propylene, isopropylene, butylene,
isobutylene, pentylene, hexylene, heptylene, octylene,

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nonylene, decylene, nonadecylene, undecylene, dodecylene, tridecylene, tetradecylene, pentadecylene, hexadecylene, heptadecylene, octadecylene, and the like.

As used herein, the term "saccharide", "saccharose", "sugar", and the like, refers to a mono-, di-, tri-, or higher order saccharide or oligosaccharide. Representative monosaccharides include glucose, mannose, galactose, glucosamine, mannosamine, galactosamine, fructose, glyceraldehyde, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, gluose, idose, talose, psicose, sorbose, and tagatose. Exemplary disaccharides include maltose, lactose, sucrose, cellobiose, trehalose, isomaltose, gentiobiose, melibiose, laminaribiose, chitobiose, xylobiose, mannobiose, sophorose, and the like. Certain tri- and higher oligosaccharides include raffinose, maltotriose ,isomaltotriose, maltotetraose, maltopentaose, mannotriose, manninotriose, etc. Exemplary polysaccharides include starch, sodium starch glycolate, alginic acid, cellulose, carboxymethylcellulose, hydroxyethylcellulose, hydropropylcellulose, hydroxypropylmethylcellulose, ethylcellulose, carageenan, chitosan, chondroitin sulfate, heparin, hyaluronic acid, and pectinic acid.

As used herein, a "saccharide residue" further refers to a saccharide molecule having at least one pyranose or furanose ring. Also, at least one hydrogen atom is removed from a hydroxyl group of the isolated saccharide molecule, as when that group has been esterified.

The term "lower alkyl group" as used herein refers to a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, and the like.

A "(meth)acrylate", as used herein refers to an α-vinylic carboxylate, e.g., a (meth)acrylic acid in which

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the acidic hydrogen atom has been replaced. Representative (meth)acrylic acids include acrylic, methacrylic, α-chloroacrylic, α-cyano acrylic, α-ethylacrylic, maleic, fumaric, itaconic, and half esters of the latter dicarboxylic acids.

The amount of (meth)acrylate used relative to saccharide in the reactions depicted in Fig. 1 is not specifically limited and is about 1 to about 10 moles, preferably about 1 to about 6 moles, per mole of saccharide.

Typically, a reaction of the present invention is conducted in aqueous solvent. However, an organic solvent can be used, particularly when synthesizing hydrophobic monomers and polymers, as long as it does not adversely affect the reaction. Examples of organic solvents which can be used with the present invention include halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, chlorobenzene and the like; aromatic hydrocarbons such as pyridine, benzene, toluene, xylene and the like; and ethers such as ethyl ether, isopropyl ether, ethyleneglycol dimethyl ether, ethyleneglycol diethyl ether, diethyleneglycol dimethyl ether, dioxane, tetrahydrofuran and the like. These solvents can be used alone or in combination with another solvent if desired.

A polymerization inhibitor can be employed in the present set of reactions and is not specifically limited. Examples of useful inhibitors are p-methoxyphenol, hydroquinone monomethyl ether, hydroquinone monoethyl ether, butylhydroxytoluene, butylcatechol, benzoquinone, nitrobenzene, cupric chloride, ferric chloride, etc. An inhibitor can be used singly or in combination with one or more other inhibitors. The amount of inhibitor used is not specifically limited, and is about 0.01 to about 2% by weight, based on (meth)acrylate.

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Reaction temperatures and reaction times are not specifically limited, and can be readily determined by the skilled practitioner. For example, the reaction temperature for conducting the epoxy ring-opening reaction illustrated in Fig. 1A is in the range of about 10 to about 80°C, preferably about 20 to 50°C. The reaction time is in the range of about 15 minutes to 10 days. The reaction temperature for conducting the base-catalyzed coupling reactions illustrated in Figs. 1B and 1C is in the range of about -10 to about 50°C, preferably about 0 to 30°C. The reaction time is in the range of about 1 hour to 1 week. The reaction temperature for conducting the esterification reactions illustrated in Figs. 1C-1F is in the range of about -10 to about 50°C, preferably about 0 to 30°C. The reaction time is in the range of about 4 hours to 5 days. Standard carbamate-forming conditions can be used for the reaction shown in Fig. 1G [see, e.g., Satchell and Satchell, Chem. Soc. Rev., 4:231-250 (1975)].

A saccharide monomer of the present invention can be copolymerized with another olefin-type compound in producing a desired copolymer. Such an olefin-type compound is represented by the formula:
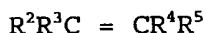
$$R^2R^3C = CR^4R^5$$

wherein R^2, R^3, R^4 and R^5 independently represent H or lower alkyl. Examples of such compounds are as follows.

(i) Hydrophilic olefin-type compounds such as 2-hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, 2-hydroxypropyl methacrylate, 2-hydroxypropyl acrylate, 2-dimethylaminoethyl acrylate or methacrylate, 2-diethylaminoethyl acrylate or methacrylate, 3-dimethylaminopropyl acrylate or methacrylate, 3-diethylaminopropyl acrylate or methacrylate, polyethylene glycol monoacrylate or monomethacrylate, acrylamide,

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methacrylamide, dimethylacrylamide, dimethylmethacrylamide, acrylic acid and its salts, methacrylic acid and its salts, N-vinylpyrrolidone, vinyl carbazole, and the like;

(ii) Hydrophobic olefin-type compounds including alkyl esters of acrylic or methacrylic acids such as methyl methacrylate, methyl acrylate, ethyl methacrylate, ethyl acrylate, butyl methacrylate, butyl acrylate, amyl methacrylate, amyl acrylate, hexyl methacrylate, hexyl acrylate, octyl methacrylate, octyl acrylate, decyl methacrylate, decyl acrylate, undecyl methacrylate, undecyl acrylate, lauryl methacrylate, lauryl acrylate, stearyl methacrylate, stearyl acrylate, cycloalkyl esters of acrylic or methcrylic acids such as cyclopentyl acrylate or methacrylate, cyclohexyl acrylate or methacrylate, other vinyl compounds such as styrene, vinyl acetate, vinyl propionate, nitriles such as acrylonitrile, etc.;

(iii) Polyfunctional olefin-type compounds such as ethylene glycol diacrylate or dimethacrylate, diethylene glycol diacrylate or dimethacrylate, triethylene glycol diacrylate or dimethacrylate, triethylene glycol diacrylate or dimethacrylate, poly(ethylene glycol) ethylether acrylate or methacrylate (PEGEEM), propylene glycol acrylate or methacrylate, poly(propylene glycol) acrylate or methacrylate (PPGM), vinyl acrylate or methacrylate, allyl acrylate or methacrylate, divinylbenzene, diallylphthalate, trimethylolpropane triacrylate or trimethacrylate, and the like.

A polymerization reaction of the present invention can be conducted by conventional methods such as mass polymerization, solution (or homogeneous) polymerization, suspension polymerization, emulsion polymerization, radiation polymerization (using γ-ray, electron beam or the like), or the like.

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For example, a solution polymerization is performed in a solvent in the presence or the absence of a polymerization initiator. Useful initiators are not specifically limited insofar as they are soluble in a
5   solvent. Examples of such initiators are organic solvent-soluble initiators such as benzoyl peroxide, azobisisobutyronitrile (AIBN), di-tertiary butyl peroxide and the like, water soluble initiators such as ammonium persulfate (APS), potassium persulfate and the like,
10   redox-type initiators which are combinations of such initiator and TEMED, Fe^{2+} salt, sodium hydrogensulfite or like reducing agent, etc. Solvents for use in a polymerization reaction of the present invention are not specifically limited as long as they can dissolve the
15   polymers. Examples of such solvents are water, alcohol, dimethylsulfoxide (DMSO), dimethylformamide (DMF), formamide, and mixtures thereof.

No specific restriction is placed on the mixing ratio of the monomer component, polymerization initiator
20   and solvent to be used in the invention. Preferable to use are less than about 5 parts by weight of the polymerization initiator and an excess amount, preferably about 200 to about 2000 parts by weight, of the solvent, per 100 parts of the monomer component.

25   The polymerization reaction is preferably conducted in the absence of oxygen. Oxygen can be removed from the reaction system as by usual atmosphere-replacing means such as degassing, nitrogen replacement, and the like. The polymerization reaction is carried out at about 0° to
30   about 90°C, preferably about 20 to 60°C, and is completed in about 20 seconds to 24 hours.

After completion of polymerization, the polymer of the invention can be separated or collected from the reaction product and purified by usual methods. For
35   example, it can be collected by admixing the reaction product with a poor solvent to precipitate the polymer.

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A thus obtained polymer of the invention has a molecular weight ranging from hundreds to millions of daltons. The compressibility of a foam prepared according to the principles of the present invention ranges from about 4,000 g/in to about 40,000 g/in.

No specific restriction is placed on a crosslinking agent for use with the present invention, as long as it can crosslink propagating saccharide-(meth)acrylate chains. Examples of useful crosslinking agents are organic polyfunctional isocyanate compounds, polyfunctional epoxy compounds, formalin, glycidol, melamine, silicone oligomer, etc. The amount of the crosslinking agent used is suitably selected over a wide range according to the amount of saccharide monomer desired in the polymer, and the degree of rigidity desired to be imparted to the polymer. For example, in the case of a copolymer of a saccharide-(meth)acryloyl aminocarboxylate and a polyfunctional olefin-type compound, the amount of crosslinking agent used is about 0.5 to 20 parts by weight, per 100 parts by weight of the copolymer.

As discussed hereinbelow, sucrose based hydrophilic and hydrophobic foams which can swell extremely fast have been synthesized and characterized. The most common foaming methods include: thermal decomposition of chemical agent, mechanical whipping, mechanical blowing, volatization of low-boiling liquid, chemical reaction, expansion of dissolved gas upon pressure release, incorporation of microsphere into a polymer mass, and expansion of gas-filled beads by heating. $NaHCO_3$ is preferably used as described herein to generate gas upon reaction with acid.

Existing superabsorbents used in baby diapers are made by a complicated method [U.S. Patent No. 5,149,335, issued to Kellenberger, et al.] and it involves the use of organic solvents which may raise safety and

environment concerns. The method of making sucrofoams described herein can be used to make a wide array of synthetic or natural foams which may be used to replace existing superabsorbents in certain circumstances.

5   Sucrofoams, including other hydrogel foams, are easy to make and show a number of superior properties to the existing products, especially in their swelling rate.

We have also examined various sucrose derivatives to prepare themoreversible hydrogels by copolymerization

10   with hydrophobic comonomers. Sucrose was chosen as a key compoment for this purpose, primarily because it has unique properties in comparision with other natural and synthetic organic reagents. Specifically, sucrose is degradable and absorbable in the body. The hydroxyl

15   groups of sucrose not only serve as good reaction sites for chemical modifications but also make the carbohydrate very water-soluble. The design of sucrose monomers is focused on balancing the hydrophilic and hydrophobic properties so that the synthesized sucrogels exhibited

20   inverse thermosensitivity resulting from the presence of lower critical solution temperature (LCST).

Swelling Ratio

The swelling ratio, Q, is an important parameter for hydrogels and hydrogel foams. It is defined as:

25       $Q = (W_s - W_d) / W_d$

where W_s and W_d are the weights of swollen gel and dried gel, respectively. In addition to the conventional measuring method, we proposed three new methods of measuring Q, each of them having their own advantages and

30   limitations.

Conventionally, W_s is measured by taking the hydrogel out of the swelling medium, gently blotting the hydrogel to remove the excess surface water, and weighing it on a balance. This method is now used by most

35   researchers [Huglin, M, et al. (1984); Davis, T., et al.

(1988); Garcia, O., et al. (1994); Jin, X., et al. (1995)]. Its advantage is its flexibility. Q can be easily measured at different temperature and in different swelling media. But it is only good for the firm gels. Highly swollen gels and foams are usually very fragile. Taking them out from the swelling media without breaking them is not always easy. Some researchers measure the size of swollen gel to calculate W_s. This approach is difficult for gels with irregular geometry. Even for gels with regular geometric shape, the determination of gel boundary is often difficult.

1. Connector Method

We have developed a simple apparatus similar to that previously described [Dubrovskii, S.A., et al. (1990)]. Briefly, a Buchner funnel was connected to the side arm of a sealed glass bottle by a plastic tubing. The glass bottle served as a reservoir. A finely scaled 10 ml pipet was attached to the top of the glass bottle via a rubber stopper. The height of the glass bottle was adjusted so that the gels in the Buchner funnel were either immersed under water or exposed to the air. During swelling of the gels, the water was absorbed into the gel and the amount of water in the glass bottle was reduced. The reduction in water (V_0-V_1) can be accurately measured from the height of water in the pipette. The volume of water absorbed into the hydrogel (V_0-V_1) was used to calculate W_s and thus Q.

This method is good for all gels and foams since direct handling of specimen is avoided. Furthermore since each measurement is fast and simple, it is especially good for continuous measurement and swelling kinetic studies. However, since the special device needs to be set up, it is not as simple as the other methods. Moreover, the major drawback of this method is that it is not flexible. Changing swelling temperature and swelling media is very inconvenient.

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2. <u>Sieve Method</u>

In this method the specimen is placed on a sieve weighing boat which can be easily made by nylon sieve, copper wire, and Teflon tape cover. The sieve weighing boat with the specimen was immersed in swelling media. When Q is measured, the boat was taken out and paper towel was used to remove excess surface water from underneath the sieve. Then the W_s was measured by subtracting the boat weight from the whole weight.

This method is similar to the conventional method. But it avoids handling the specimen. So it is good for both firm gels and fragile gels. Also, it is flexible. It can measure Q at different temperature and swelling media. But it is not very appropriate for foam samples since the suction can take away liquid from the foam matrix.

3. <u>Titration Method</u>

In this method, the specimen is placed in a plastic weighing boat. Swelling solution was added dropwise from a buret. Titration was stopped when free flow liquid appeared. The amount of liquid absorbed was easily read from the buret. This method requires the specimen to absorb the swelling media at a very fast rate. Therefore, it is only good for measuring foam.

<u>Swelling Rate</u>

The swelling rate is a critical characteristic of hydrogels and hydrofoams. No standard measuring method, however, has been established. The existing methods are very empirical [see, U.S. Patent No. 5,149,335]. Some researchers use the time to reach equilibrium swelling as an indicator for swelling rate. The exact point to reach equilibrium swelling, however, is hard to define from the swelling kinetic curve. It is necessary to establish a standard method to compare the swelling rate of different gels and foams. Since the measurement of swelling ratio (Q) is easy and there are several methods available as

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previously mentioned, we used the time to reach half
equilibrium swelling (Thq) as the indicator of swelling
rate. From the swelling kinetic curve, this point can be
easily and accurately defined (Fig. 2).

Both polymer itself and the structural porosity
affect the swelling rate. Wetting agents, however, can
somehow change the surface properties of the gels or
foams. U.S. Patent No. 5,149,335 discloses use of
Voranol, a polyol, as a wetting agent to increase the gel
wettibility and hence increased the swelling rate. In
our foam production, Voranol (The Dow Chemical Company)
was also added to the sucrofoams to improve the swelling
performance.

PART I. Hydrophilic Sucrogels and Sucrofoams
Saccharide Monomer Synthesis

Three different alkylating agents, glycidyl acrylate
(GA), glycidyl methacrylate (GM), and 1,2-epoxy-5-hexene
(EH) were used to modify sucrose in aqueous solution.
Since GM and EH are more hydrophobic than GA, the
heterogeneous reaction proceeds very slowly in aqueous
solution. Therefore, GA was chosen for the subsequent
studies. Tetrabutyl ammonium bromide (TAB), a phase
transfer catalyst, was found to greatly accelerate the
heterogeneous reaction. But when TAB was used, the pH
had to be adjusted to ensure its best performance. The
reaction at pH 7.2 was faster than that at pH 6.0 or 9.0.
In addition to catalyst and pH, the reaction could also
be controlled by changing the reaction ratio, stirring
rate, and reaction temperature.

As depicted in Fig. 1 and described in Example I-1,
a saccharide (sucrose) reacts with glycidyl acrylate in
aqueous solution by opening the epoxy ring to produce a
saccharide-GA monomer. The mass spectrum of S-GA
monomers so produced, however, showed the presence of a
transesterification product. Also, from TLC analysis of

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the S-GA monomers, the presence of ring-opened GA and acrylic acid was observed. Thus, at least four competing reactions are involved in the S-GA synthesis. The presence of acrylic acid (AA) makes the swelling of gels pH-dependent as described hereinbelow.

The degree of substitution (DS) of glycidyl acrylate (GA) modified saccharides was measured by the bromine method [Edman, P., et al. (1980); Hoppe, H., et al. (1977)] or by the proton-NMR method [Lepisto, M., et al. (1983)]. The proton-NMR method was not very accurate because many peaks were crowded in a small spectral window; however, quantitative C-13 NMR spectroscopy has been suggested as a potential tool for determining the degree of substitution [Akoh, C.C., et al. (1987); Akoh, D.C., et al. (1989)].

The extent of reaction of the S-2.5d monomer was determined from the quantitative C-13 NMR spectrum (see Example I-2) Due to side reactions, the exact degree of substitution could not be obtained from the spectrum. However, by comparing the average peak area of two vinyl carbons (129 and 137 ppm) with the anomeric sucrose carbon at 106 ppm, the extent of reaction could be estimated. Table 1 shows the extent of reaction determined for the four S-GA monomers studied.

Table 1.
    Extent of reaction of S-GA monomers estimated by quantitative C-13 NMR spectra.

	Extent of reaction
S-3h (sucrose: GA=1:4)	0.20
S-1.5d (sucrose: GA=1:1.5)	0.35
S-2.5d (sucrose: GA=1:1.5)	0.47
S-10d (sucrose: GA=1:8)	6.7

25

The monomers were then polymerized to product
hydrophilic sucrogels. (Example I-3)

S-GA Gel Swelling

Fig. 3 shows the swelling kinetics of S-2.5d gels
in distilled deionized water (DDW), 0.9% NaCl, and 0.03
M HCl solution. These studies were performed as
described in Example I-4. The swelling ratios and
swelling rates are compared with the S-2.5d foams in
Table 2. In saline and HCl solution, the swelling
ratios of the gel were lower than those in water. This
is believed to be because the side-product AA is also
incorporated into the gels - its negative charge at
neutral pH caused the gel to swell to a larger extent.

Table 2.
        Comparison of the swelling ratio (Q) and swelling
        rate (Thq) of sucrogels and sucrofoams with
        different degree of modification.

		S-10d		S-2.5d		S-1.5d		S-3h	
		gel	foam	gel	foam	gel	foam	gel	foam
In DDW	Q	1.02	9	5.2	52	12	98	27	200
	Thq		4 sec	1.2 h	2 sec		2 sec		3 sec
In 0.9% NaCl solution	Q			3.4	33		50		
	Thq			1.1 h	2 sec		4 sec		
In pH 1.5 HCl solution	Q			2.8					
	Thq			1.2 h					

The swelling properties of foams and gels are
compared in Table 2. The foams and gels had big
differences in their swelling ratios and swelling
rates. Under the same swelling condition, foams
usually swelled about 7-10 times larger than the gels.
This remarkable difference was due to the unique
structural characteristics of the foams. The foams

contain numerous empty cells which are dispersed throughout the polymer matrix. When the foams swell in aqueous solution, not only the polymer chains expand with the uptake of water, as in hydrogels, but also

5 numerous empty cells expand to even larger sizes. This accounts for the much higher Q value of foams than hydrogels.

Table 2 also shows that the swelling rates (Thq) of sucrogels and sucrofoams differ greatly. For the

10 gels tested, more than one hour was needed for them to reach the half equilibrium. For the foams, however, only a few seconds were needed. The fast swelling rate of sucrofoams made it difficult to study their swelling kinetics.

15 There are several factors which contribute to the fast swelling property of foams. First, from the SEM pictures it was observed that the majority of the cells are open cells. These cells are connected to each other throughout the polymer matrix and acted as

20 numerous capillary channels. When the dried foams are placed in aqueous solution, water flows rapidly into the capillary channels and swells the foam. This capillary effect does not exist in ordinary hydrogels.

Kellenberger et al. [U.S. Patent No. 5,149,335]

25 tried to connect many small hydrogel particles together to form larger particles. By this process, they reportedly introduced some capillary channels into the large particles and greatly increased the swelling rate of the hydrogel particles. However, this method is

30 complicated and only limited capillary channels were introduced. Therefore, the swelling rates of these hydrogel particles were still lower than that of the foams of the present invention. The other important factors which contribute to the fast swelling of

35 hydrofoams are the greater diffusion surface area created by the empty cells and the shorter diffusion

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distance caused by the very thin cell wall. The
swelling process cannot be faster than a diffusion
process.

The total amount of solution diffused in the
polymer within a unit time (M/t) is proportional to the
available diffusion surface area S and inversely
proportional to the diffusion distance h:

$$(M/t \propto S/h)$$

Since the foams have much larger total surface area S
and shorter diffusion distance h, the rate of diffusion
of the foams is greatly increased compared with the
gels. For the same reason, microsphere hydrogels,
having larger surface area and shorter diffusion
distance because of their small diameter, can swell to
equilibrium within a few minutes compared to the hours
required for the larger size hydrogels [Tomlinson, E.,
et al. (1985)]. However, foam swelling includes
another process before the diffusion, which is that
water flows through the capillary channels and reaches
all the surface area. Alcohol dehydration and the
wetting agent enhance the rate of flowing. In fact,
some foams swelled so fast that the limiting step in
swelling is not the diffusion step but the flowing
step.

The crosslinking density can also affect the
swelling ratio Q. S-10d foams and gels had higher
crosslinking density because they had a higher degree
of substitution. The Q value of S-10d foams and gels
was much lower than the other three samples. Table 2
shows that the swelling ratio decreases with the
increase of substitution. Table 2 also shows that the
Q value decreases in saline solution and in acidic
solution. This was due to the incorporation of AA in
the polymer matrix.

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S-GA Foam Synthesis

  In the synthesis of foams, surfactants were used
not only as a foaming agent but also as a foam
stabilizer. A good foam stabilizer should be able to
lower the interfacial tension and increase the
interfacial film viscosity [Hartley, F.D., et al.
(1968)]. These studies are described in more detail in
Example I-5. The foaming and foam stabilizing
abilities of Pluronic F-127, BSA, and SDS were compared
using S-2.5d monomer solution (See Table 3 and Example
I-6).

Table 3.
  Comparison of Pluronic F-127, BSA, and SDS as
  surfactant in S-GA monomer solution. (The
  solution volume before foam was 0.53 ml)

Final surfactant concentration (%)	Foam volume (ml)		
	Peak volume	At 1 min	At 5 min
Control	1.4	0.53	0.53
Pluronic F-127			
0.05	4.6	3.8	0.62
0.1	4.8	4.6	0.71
0.2	4.8	4.6	0.80
0.35	4.5	4.3	0.98
0.5	4.5	4.3	1.04
0.75	4.5	4.3	1.03
BSA			
0.01	4.3	1.0	0.53
0.02	4.4	2.1	0.53
0.05	4.6	3.7	0.62
0.1	4.6	3.8	0.63
0.25	4.6	3.8	0.62
SDS			
0.05	1.2	0.53	0.53
0.1	1.1	0.53	0.53
0.2	1.1	0.53	0.53
0.5	2.1	0.53	0.53
1	2.2	0.80	0.53

  The peak foam volume represents the foaming
ability. Larger peak foam volume suggests a better

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foaming agent. The foam volumes at 1 minute and 5
minutes reflect the foam stabilizing ability. The
longer the foam is sustained, the better foam
stabilizer the surfactant is. All three surfactants
5   showed better foaming and foam stabilizing properties
compared to the control. SDS, however, was a poor
foaming agent and foam stabilizer in the S-GA monomer
solution.

Both Pluronic F-127 and BSA were good foaming
10   agents as shown from the peak foam volumes, which were
several times larger than the volume of the starting
monomer solution. Pluronic F-127, however, was proved
to be a better foam stabilizer. At 0.5%, foam did not
subside much after 1 minute. Even after 5 minutes, the
15   volume of the foam was still twice that of the starting
solution. BSA could only sustain the foam for 1
minute. After that the foam subsided rapidly. From
Table 3 it is also seen that at lower concentrations of
surfactants, the increase in the surfactant
20   concentration improves the foaming and foam stabilizing
effect. But above a certain level, more surfactant
does not result in more improvement.

In the S-GA foam synthesis, $NaHCO_3$ was used not
only as a blowing agent, i.e., it reacts with acid to
25   release CO_2, but also as a pH neutralizer.
Polymerization at room temperature using APS and TEMED
is pH-dependent. The optimal pH for the initiators is
around pH 7-8. The addition of AA reduces the pH to an
acidic level which inhibits the initiation of
30   polymerization. Therefore in the absence of $NaHCO_3$,
the polymerization proceeds at a very slow rate. This
is best shown by the A-B period in the polymerization
curve (Fig. 4-A). Upon the addition of $NaHCO_3$, both
foam and pH start rising (D-E on the foaming curve),
35   and the polymerization proceeds rapidly (B-C on the
polymerization curve).

30

Fig. 4-A shows two processes, foaming and polymerization, occurring during the foam synthesis. These two processes must be carefully balanced to make foams successfully. First, the polymerization kinetics

5   must be fast. Since the foam stabilizer can only sustain the foam for a few minutes (E-F on the foaming curve), if the polymerization cannot be completed in such a short time, the foam will subside and the gas bubbles will escape (Fig. 4-B). This usually results

10   in smaller foam size or even the formation of gel instead of foam. To achieve fast polymerization kinetics, a good chemical initiator must be used. APS used in our experiment is a very fast initiator when catalyzed by TEMED. Higher reaction temperature and

15   high monomer concentration also help to facilitate the polymerization. Two other circumstances may cause a similar problem. In Fig. 4-A, foaming and polymerization started simultaneously, but in most cases the foaming and polymerization do not begin at

20   the same time. If foaming starts too early, the polymerization may not be fast enough to entrap the gas bubbles. If the foam stabilizer is not very efficient (i.e., the E-F period is too short), the polymerization curve may easily fall behind the foaming curve.

25   If the foaming curve falls too far behind the polymerization curve, a good foam cannot be synthesized either (Fig. 4-C). This can happen if $NaHCO_3$ is added too late so that polymerization approaches the end. Since very few gas bubbles are generated, the product

30   is essentially a gel with a few closed cells in it. On the other hand, if too much blowing agents (both acid and $NaHCO_3$) are added, there is still a lot of gas generated even when polymerization approaches the end. The excess amount of gas will make the cell wall thin

35   and eventually destroy the foam. The foams formed

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under this condition usually have large internal void
volumes.

In summary, successful synthesis of foams requires
careful control of the foaming and polymerization
processes in such a way that the polymerization point C
falls within foam stabilizing phase E-F (Fig. 4-A). To
realize this, the control of timing is critically
important. A good surfactant can extend the duration
of E-F, and this will make the timing control easier.
The formulation in Example 5 was carefully chosen to
meet all the requirements to make a good S-GA foam.
Several synthetic hydrophilic foams (poly(acrylic acid)
foam, polyacrylamide foam, poly(hydroxylpropyl
methacrylate) foam) were also successfully synthesized
by the same formulation with only slight adjustment.
It should be noted that only monomers having fast
polymerization kinetics can be used for this method.

Acrylic acid (AA) was used in the foam synthesis.
It reacted with $NaHCO_3$ to release fine CO_2 gas bubbles
and inflate the foam. AA itself, however, can also be
incorporated into the polymer matrix. Its negative
charge may change the swelling properties of the foam.
Table 4 shows the effect of AA on the foam properties.
65 μl of 6 N HCl and 30 μl of AA could raise the foam
to the same height. The resulting foams showed no
difference in their density and swelling rate, Thq.
Both swelled extremely fast, but foams formed with AA
showed larger Q (swelling ratio) in both water and in
0.9% NaCl solution. This observation is attributed to
the electrostatic force caused by the negatively
charged AA. Even for the foams blown by HCl, Q in
water was larger than that in NaCl solution. This is
also attributed to a small amount of AA in the S-2.5d
monomer solution.

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Table 4.
       Effect of blowing agent on the properties of S-
       2.5d foams.

Blowing agent	Density of the dried foam (g/cm³)	Q in 0.9% NaCl solution	Q in DDW	Thq (sec)
30 µl of AA	0.11	34	53	2
65 µl of 6 N HCl	0.11	22	41	2

In addition to the type of acid, the amount of the
acid is also important for the foam properties. These
studies are described in Example I-7. Table 5 shows
the effect of the amount of AA on the foam properties
when the amount of $NaHCO_3$ was maintained constant (42
mg). As the amount of AA increased, the foam became
larger so the dried foam size became larger and the
density became smaller. As shown in Table 5, Q
increased when more blowing agent was used. This was
because more empty spaces were generated in foams with
more blowing agent. Therefore, these foams could
absorb more water and resulted in higher Q. This
resulted in a higher swelling ratio.

Table 5.
       Effect of the amount of acrylic acid on the foam
       properties. (Swelling ratio was measured in 0.9%
       NaCl solution)

Acrylic acid (ul)	Peak foam size (ml)	Dry foam density (g/cm³)	Swelling ratio
5	1.0	0.60	10.4
10	1.6	0.30	16.9
15	2.5	0.12	33.7
30	4.2	0.09	50.6
50	6.5	0.07	58.0
80*	8.1	0.53	16.0

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The foams were studied with SEM to determine the
effects on their structure of using different amounts
of AA. Foams made with 80 μl AA had an average pore
diameter of 530 μm, which was much larger than that of

5   foams made with 30 μl AA, i.e., 180 μm. The same
results were observed when HCl was used as blowing
agent, i.e., more HCl caused lower foam density and
higher Q. Foams made with 80 μl of AA did not follow
the same trend. In this case, 80 μl of AA was reacted

10   with 42 mg of NaHCO$_3$ and more gas bubbles were released
making the initial foam size larger than all the
others. But since AA was in excess after being reacted
with NaHCO$_3$, the pH of the solution was very low. This
greatly decreased the polymerization rate. Therefore,

15   the foam raised, subsided and eventually collapsed
before the polymerization finished. This process is
described in Fig. 4-B where gas bubbles cannot be
entrapped in the polymer matrix. For this reason, the
density of foams with 80 μl of AA was higher and Q was

20   lower than foams with 50 μl of AA. Since keeping the
solution at higher pH is important to guarantee a fast
polymerization rate, an excess amount of NaHCO$_3$ should
be used. However, even if a higher pH is maintained,
too much gas will weaken the cell wall and even destroy

25   the foam structure as described in Fig. 4-C. Thus, the
total amount of blowing agent should be adjusted
accordingly.

During the foam synthesis, ingredient A was added
to B as described in the Examples. This particular

30   sequence was preferred to make a good foam. When acid
solution A was added to NaHCO$_3$ in B, the gas bubbles
started from the test tube bottom. Good mixing was
achieved and a uniform foam could be easily made. If
the sequence was reversed, gas bubbles started from the

35   solution surface, and it would be hard to mix the

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solution well. Gel instead of uniform foam was usually
formed at the bottom of the test tube.

Pressure can affect the foam structure, too, as
shown by the studies described in Example I-9. Under
5   pressure, less gas bubbles are released. Therefore,
the pore size will be smaller. For instance, the
average cell diameter of a S-2.5d foam made in the
capped test tube with 80 μl of AA was about 320 μm, as
compared with the cell diameter of about 530 μm
10   obtained under atmosphere pressure.

Alcohol dehydration plays an important role in
ensuring the fast swell of foams as shown in Example I-
10. If a foam is air dried after washing in water, the
foam shrinks to a small condensed piece due to the high
15   surface tension of water (72 dyn/cm at room
temperature). The polymer chains collapse and close
some of the capillary channels. On the other hand,
alcohol has a lower surface tension (22 dyn/cm at room
temperature) and is a nonsolvent to the S-GA foam.
20   After the dehydration process, water is replaced by
alcohol and the polymer chains precipitate in the
alcohol and became hardened. The drying process then
does not greatly change the foam size. Foams formed in
this way had larger pore size and lower density. The
25   average pore size of S-1.5d foam treated with alcohol
was much larger than the same foam without alcohol
treatment. The number and the size of pores were much
greater and this created a great capillary effect.
Besides, more and larger pores created much larger
30   total surface area available for diffusion. Also, the
cell wall was much thinner and this is expected to
provide a shorter diffusion distance. All these
accounted for the fast swelling of S-1.5d foams treated
with alcohol (Thq = 2 seconds when swollen in water)
35   and very slow swelling rate of the foams without
alcohol treatment (Thq = ~ 14 minutes when swollen in

water). The latter foams still showed faster swelling
than the gels (Thq = ~ 1.2 hours when swollen in water)
which swelled as a result of diffusion of water through
the gel surface.

5   Wetting agents can change the surface wettibility
of foams. As disclosed in U.S. Patent No. 5,149,335,
Voranol (a polyol) was used as a wetting agent to
increase the swelling rate of polyacrylate hydrogel
particles. In the present studies, 1% Voranol 240-800

10   was found to increase the swelling rate of S-3h foam
(Table 6).

Table 6.
       Effect of wetting agent (Voranol 240-800 1% in
       alcohol) on the swelling rate of foams in 0.9%

15   NaCl solution.

	Thq of foams with wetting agent	Thq of foams without wetting agent
S-3h foam	3 sec	6 sec
S-2.5d foam	2 sec	2 sec

       No improvement was observed for S-2.5d foams. The
exact reason for this is not clear yet. In another

20   experiment, Voranol greatly improved the swelling rate
of polyacrylamide foams.

Degradation of Gels and Foams
       As pointed out previously [Straathof, A.J.J., et
al. (1988)], sucrose will not be degraded by invertase

25   as is natural sucrose whenever the fructose ring of the
sucrose molecule is modified. In the present studies,
sucrogels and sucrofoams were not degraded by
invertase, lipase, dipase, acylase, or protease (XXIII)
(all from Sigma). In acidic condition, the degradation

30   was slow. No degradation was observed for S-2.5d and
S-3h gels even after 2 weeks in 0.1 N HCl at 37°C
(Table 7). A stronger hydrolysis condition, 0.1 N HCl

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at 90°C, was employed for accelerating the hydrolysis
in order to have a rapid understanding of its
degradability. These studies are described in Example
I-11.

5   Table 7.
            Degradation time of S-3h gels, S-2.5d gels, and S-
            2.5d foam under different conditions.

	0.1 N HCl 37°C	0.1 N HCl 90°C	DDW 90°C	0.03 N NaOH 37°C
S-3h gels	no	3 days	9 days	4 hr
S-2.5d gels	no	9 days	no	10 days
S-2.5d foams	no	8 days	no	3 days

10

        In 0.1 N HCl solution at 90°C, the lower
crosslinked S-3h gels degraded within 3 days, whereas
the higher crosslinked S-2.5d gels degraded after 9
days. Even the S-2.5d foams degraded very slowly in
15   acidic solution. In DDW, only S-3h gels which had very
low crosslinking density degraded after 9 days at 90°C.
In basic solution, the degradation process was much
faster. In 0.03 N NaOH solution, S-3h gels degraded
within 4 hours at 37°C. However, S-2.5d gels, which
20   had higher crosslinking density, still needed 10 days
to degrade completely. In contrast, the S-2.5d foams
degraded much faster - 3 days in the same solution.
        Fig. 5 depicts the degradation kinetics of the S-
2.5d gels and foams. Gels or foams first swelled to
25   absorb the basic solution. Then, as the degradation
progressed, some of the crosslinkers were cleaved.
This resulted in a lower crosslinking density and
higher swelling ratio. Therefore, equilibrium swelling
was never reached, i.e., they kept swelling until
30   reaching a point that they were totally dissolved. In
the degradation studies, at a certain point, the gels
or foams became so flexible that they could pass

through the sieve weighing boat used in the degradation
studies and dissolved in the basic solution. This is
why the measured swelling ratio showed a transient peak
in Fig. 5.

5   The degradation mechanism was studied in Example
I-12. The main degradation route for the S-GA gels and
foams in base, acid, or DDW is believed to be
hydrolysis. Water reacts with ester bonds in the
polymer chains, and this leads to the degradation of
10   the polymer. Both base and acid work as catalyst to
the hydrolysis. Therefore, the degradation in base or
acid is faster than in water. Base hydrolysis and acid
hydrolysis have different mechanisms. In basic
solution, the degradation occurs very fast at the ester
15   bond. In addition to the hydrolysis of the ester
bonds, acid can also cleave the ether linkage between
the glucose and fructose ring, but the acid-catalyzed
hydrolysis and ether bond cleavage are very slow.

           In summary, the degradation rate is dependent on
20   the degradation media, crosslinking density, incubation
temperature, and the polymer structure (gel or foam).
Basic solution, lower crosslinking density, higher
temperature, and foam can promote the degradation.

<u>Compressibility of Foams</u>

25   Compressibility is an important characteristic for
practical application of foams. It represents the
pressure endurance of foams after absorbing certain
amounts of water. The method used in this study is
described in Example I-14, and is a simple way to
30   compare the pressure endurance of different foams.
Even though the S-3h foam had a higher swelling ratio
(200 in DDW) than S-1.5d foam (98 in DDW), its
compression coefficient, K, was lower than that of S-
1.5d foam (Table 8). This meant that it had less
35   pressure endurance. This is believed because its

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crosslinking density is too low to support the foam
under pressure. The S-2.5d foam had a lower K value
than the S-1.5d foam even though the former had a
higher crosslinking density. This is because its
swelling ratio was too low (52 in DDW) to hold water
tightly. Under pressure, even though the S-2.5d foam
did not break, the water was squeezed out. To make
foams with a higher pressure endurance, the
crosslinking density and the swelling ratio must be
properly balanced. Too high or too low a crosslinking
density will lead to less pressure endurance.

Table 8.
    Compressibility study of sucrofoams. K, an
    indicator of the pressure endurance, was
    calculated by $\Delta W/\Delta D$.

	weight range (g)	ΔW (g)	ΔD (in)	K (g/in)
S-3h foams	110-210	100	0.014	7100
S-1.5d foams	110-210	100	0.003	33000
S-2.5d foams	110-210	100	0.024	4200

II.   Hydrophobic Sucrogels and Sucrofoams
Saccharide Monomer Synthesis

       As described in Example II-1, sucrose is reacted
with methacrylol chloride and acetyl chloride to make
hydrophobic sucrose monomers. An unsuccessful attempt
was made to use acrylol chloride instead of methacrylol
chloride because acrylate had a faster polymerization
rate than methacrylate. But as shown previously
[Hickmott, P.W. (1964)], acrylol chloride reacts with
alcohols (ROH) in the presence of pyridine in a
different way from methacrylol chloride. The main
product is a pyridine salt.

       The degree of substitution (DS) of sucrose
monomers can be easily controlled by changing the
reaction ratio of sucrose to methacrylol chloride or

acetyl chloride. In the present study, two batches of
sucrose monomers, S-H and S-L, were synthesized with
higher and lower DS, respectively.

As described in Example II-2, the approximate DS
of the S-H monomer was determined from the ^{1}H NMR and
quantitative C-13 NMR sprectra. From the CH_3 group at
18.2 ppm and 20.6 ppm, a DS of 2.25 for methacrylate
and 4.74 for acetate was calculated. From the vinyl
carbons at 126 and 136 ppm, the DS of methacrylate was
found to be 2.46 (average of the two vinyl peaks).
From the carbonyl peaks, the DS of methacrylate was
calculated as 2.27, whereas the DS of acetate as 4.69
(Table 9).

Table 9.
   Degree of substitution (DS) of methacrylate and
   acetate groups on S-H and S-L monomers (calculated
   by quantitative C-13 NMR and proton NMR).

		quantitative C-13 NMR			proton NMR
		from methyl	from vinyl	from carbonyl	from vinyl
S-H monomer	methacrylate	2.25	2.46	2.27	2.35
	acetate	4.74		4.69	4.91
S-L monomer	methacrylate	0.93	0.95	0.83	0.80
	acetate	3.63		3.64	3.85

The DS of the S-L monomer was characterized by the
same method. The results given in Table 9 show that
the DS calculated from different peak integrals were
very close. Quantitative C-13 NMR spectra, however,
provided clearer peaks (no overlap) and more structural
information than the proton NMR spectra.

Characteristic infrared (IR) absorption bands were
observed at 3485 cm^{-1} (O-H stretch), 3000-2850 cm^{-1} (C-H
stretch), 1751 cm^{-1} and 1726 cm^{-1} (ester C=O stretch).
The IR spectral data confirmed the structure of the S-H
monomer. The O-H stretch at 3485 cm^{-1} was greatly

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decreased in contrast to pure sucrose. This was because, on average, more than 7 out of 8 -OH on sucrose were modified by either methacrylate or acetate (from the NMR data). Less than one free hydroxyl group was left on each sucrose molecule. The C=O ester bond absorption at 1751 cm^{-1} was the acetate carbonyl. This peak was larger than the ester bond absorption peak of methacrylate at 1726 cm^{-1}. This also conformed to the fact that the DS of acetate was larger than that of methacrylate.

S-H and S-L monomers were easily converted to gels in organic solvents using either chemical or irradiation initiation. These studies are described in Example II-3.

Foam Formation

Both S-H and S-L monomers were not water soluble. In order to make good sucrofoams from these monomers, a good solvent had to be chosen first to dissolve all the ingredients involved in the foam formation. As illustrated above, several requirements must be met to form a good foam. First, fast polymerization kinetics is needed. Thus careful selection of a good initiator system is important. APS and TEMED were used as an initiator system since they showed faster polymerization kinetics than the other initiators (e.g., azo initiators). Higher reaction temperature and higher monomer concentration were also used to increase the polymerization rate. Second, a proper surfactant system with good foaming and foam stabilizing ability must be selected. Third, the acid used to generate gas bubbles is different in different solvent system. Acrylic acid used in S-GA foam could not produce CO_2 gas when reacted with $NaHCO_3$ in DMSO solution. Another factor is the control of timing. Higher temperature was used in the synthesis of

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hydrophobic foams. Under this condition, the initial
slow polymerization phase was absent. NaHCO_3 was no
longer a polymerization trigger as in the synthesis of
S-GA foam. The polymerization kinetics of the

5   hydrophobic monomers were also slower than that of the
S-GA monomers. All these made the timing control more
difficult. The best time to add the NaHCO_3 was
determined by trial-and-error to ensure that the
polymerization was completed in the foam sustaining

10   phase (E-F in Fig. 4-A).

As described in Example II-4, dimethyl sulfoxide
(DMSO) was chosen as the solvent for S-H foam
formation. It was a good solvent for the S-H monomer
and all the other ingredients. Ammonium persulfate

15   (APS) in solid form was found to accelerate
polymerization over that in solution. Foam was
synthesized at 60°C to ensure that the polymerization
was completed within a few minutes. At room
temperature, the polymerization was too slow. The

20   surfactants were chosen from the Silwet surfactant
series, Pluronic series, Triton series, Tween and Span
series. Two surfactants, Silwet L7605 and Pluronic
P105, were found to perform best. Silwet L7605,
polyalkylene oxide-modified polydimethylsiloxane, is a

25   silicone surfactant used in the polyurethane industry.
Pluronic P105 is a PEO-PPO-PEO triblock copolymer and
with the HLB value 12-18. Both surfactants are waxy
solids. Either one of them showed good foaming ability
but not very good foam stabilizing properties. But

30   when they were properly combined as described in the
Examples section, the surfactant system showed a good
foam stabilizing property. The possible reason was
that one of them worked to decrease the interfacial
tension while the other worked to make the foam film

35   tougher. In the DMSO solution, acrylic acid or citric
acid could not generate CO_2 when mixed with NaHCO_3

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powder. Thus, a stronger organic acid, p-
toluenesulfonic acid solid was used as a blowing agent.

Because the S-H monomers contained many vinyl
groups, the crosslinking density of the foam was very
high. Therefore, the synthesized foams were brittle as
well as fragile, and swelled little in water, methanol,
ethanol, acetone, chloroform, and toluene. For this
reason, S-L foams which had a lower DS were
synthesized. S-L monomer had a lower degree of
substitution and was less hydrophobic. Isopropanol was
found to be a good solvent to make S-L foam. Silwet
L7605 and Pluronic F-127 were chosen from a variety of
surfactants and showed best properties. The foams were
formed at even higher temperature, 85°C, to ensure fast
polymerization. However, the curing was carried out at
room temperature. In the synthesis of S-L foams, if
curing was carried out at high temperature, more gas
would be released and the gas releasing would last even
when the polymerization approaches the end. This could
destroy the foam structure as shown in Fig. 4-C. In
the isopropanol solution, acrylic acid or HCl was used
as blowing agent. The swelling ratio Q of S-L foams
was 12 in both DDW and 0.9% NaCl solution when HCl was
used as a blowing agent. Q was measured by the
titration method. This suggested that there was no
charge in the polymer matrix. The swelling rate, Thq,
in DDW were 10 seconds and 27 seconds with and without
the wetting agent treatment, respectively. Thq was
measured as described above. Wetting agent increased
the swelling rate of the S-L foams, but even with the
wetting agent, S-L foams still swelled much slower than
those hydrophilic foams (Table 2). The S-L foam was
studied by SEM.

As further described in Example II-4, copolymer
foams were synthesized by a method similar to the S-L
foams. The same surfactants (Silwet 7605 and Pluronic

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F-127) were used but with a different ratio. HCl was
used as a blowing agent. Unlike the open cells
observed previously, most of the cells of the copolymer
foam were closed. The average pore size was about 150
5   μm which was smaller than that of the other foams.
This can be explained by fact that less gas was
released due to less acid being used.

Degradation of Foams

        S-L foam showed little degradation in 1 N HCl
10   solution at 90°C even after one month, but in 1 N NaOH
solution at 90°C, it was degraded within 12 hours.
These studies are described in Example II-5. Fig. 6
illustrates a TLC plate showing the degradation
mechanism in acidic and basic solution. Spot A was
15   pure sucrose. Spot B was the degradation products
(glucose and fructose) of sucrose in acid. Spot C was
the spot of sucrose after being incubated in basic
solution. It showed that sucrose was not degraded by
basic solution. Spot D was the hydrophobic S-L
20   monomer. Spot E was the degradation product of S-L
foam in 1N HCl. Even though the degradation was not
significant, it still showed some spots the same as the
degradation products of sucrose in acidic solution.
This suggested the degradation mechanism involved both
25   the ester bond cleavage and the ether bond (between the
glucose and fructose ring) cleavage in acid. If only
the second mechanism existed, the degradation products
should have contained glucose acetate and fructose
acetate which had higher rf value than the sucrose.
30   These spots were not observed on the TLC plate. From
the TLC study, however, we could not confirm whether
these two mechanisms worked simultaneously or the ether
bond cleavage happened only after the ester bonds were
cleaved. Spot F was the degradation product of S-L
35   foam in a basic solution. Sucrose was the final

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degradation product. This meant the ester bond
hydrolysis was the only mechanism in basic solution.
Since the base catalyzed hydrolysis had much higher
kinetics, the degradation of S-L foam in base was much
5   faster.

        III. Thermoreversible Saccharide Monomers
        Synthesis of S-N-methacryloyl aminocarboxylate monomers
             Two separate reactions were used in the synthesis
        of thermoreversible saccharide monomers, as exemplified
10   with sucrose. First, substituents that esterify
        sucrose are obtained. The method of controlling the
        hydrophobicity of substituent molecules was considered,
        since hydrophobic properties are necessary to make
        thermoreversible hydrogels.
15   Sucrose substituents can be synthesized fast and
        with ease by the Schotten-Bauman reaction. As shown in
        Example III-1, under basic conditions, methacryloyl
        chloride reacts with amine groups of 6-aminocaproic
        acid, leucine, and 11-aminoundecanoic acid to form
20   amide bonds. The choice of N-amino carboxylic acids
        with various carbon lengths made it possible to control
        the hydrophobicity of sucrose monomers to a certain
        extent. One practical advantage of this approach is
        that various amino acids can be utilized for the
25   preparation of sucrose monomers having different
        properties.
             In the second step, the substituents are reacted
        with sucrose by the Mitsunobu reaction. Advantages of
        the Mitsunobu reaction in the esterification of sucrose
30   have been discussed previously [Abouhilale, S., et al.
        (1991)]. The Mitsunobu reaction does not require that
        the medium be basic which generally results in
        undesirable side-reactions such as acyl migration. The
        Mitsunobu reaction proceeds fast even at room
35   temperature and esterifies only primary hydroxyl

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groups. Since sucrose has three primary hydroxyl
groups, the resultant sucrose derivatives can be used
as a crosslinking agent in the synthesis of sucrose
hydrogels. This step is described in more detail in
Example III-2.

     Synthesized sucrose monomers (MACS, DMACS, MLS,
and MAUS) were characterized by NMR. Structural
formulas for these compounds are shown in Fig. 7. The
^{13}C-NMR data showed that the most favorable site for
esterification in sucrose was OH-6, since the first
substituent always reacted with it first. This
observation is consistent with the previous study
[Abouhilale et al. (1991)] who synthesized
polyfluorinated 6-esters of sucrose with the Mitsunobu
reaction. All of the carbon peaks and some proton
peaks from sucrose were identified on the basis of
their results. In the synthesis of DMACS, the molar
ratio of sucrose:N-methacryl-6-aminocaproic acid was
1:1.5. The ^{13}C-NMR spectrum of purified DMAC showed
that two N-methacryloyl-6-aminocaproyl groups were
attached to C-6 and C-6'. The C-5' peak (83.9 ppm) and
the C-6' peak (64.1 ppm) of sucrose shifted to upfield
by 3 ppm and 2.7 ppm, respectively. These shifts are
consistent with those reported elsewhere [Jansson et
al., (1987)] in the modification of glucose. The
previous results showed that the introduction of an O-
acetyl group in any position of a glycopyranoside
caused deshielding of the substituted carbon by 0.7-3.5
ppm and shielding of the carbons next to this carbons
(b carbons) by 1.2-2.8 ppm. Other evidence for the
disubstitution of DMACS was that two ester carbons were
identified by two peaks at 175.1 and 175.3 ppm.

     The degree of substitution of DMACS was also
calculated from integration of ^{1}H-NMR peaks. When a
special decoupling agent is used, ^{13}C-NMR also provides
quantitative information on the number of carbons. The

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integrated ^{13}C-NMR spectrum of DMACS showed that the
integration value of substituent carbon peaks was about
twice that of sucrose peaks. The data of elemental
analysis were also close to theoretically calculated
values.

Temperature-dependent swelling profiles

        As described in Example III-3, sucrose monomers
were copolymerized with commercially available
hydrophobic monomers such as PPGM and PEGEEM to make
thermoreversible hydrogels. The formation of hydrogels
was tested by polymerization of monomer mixtures with
different amounts of DMACS, a crosslinking agent. The
monomer mixture of MACS and PPGM formed a gel at low
concentration and even in the absence of DMACS. As
the polymerization proceeded, polymer chains containing
PPGM and MACS might entangle each other significantly
to form a gel even in the absence of DMACS. MLS which
has a leucyl group, however, needed a relatively large
amount of DMACS. At 5 mole% of DMACS, a very fragile
hydrogel of poly(MLS-co-PPGM) formed. In subsequent
studies, MACS-containing sucrogels were crosslinked
with 0.5 mole% of DMACS, while MLS-containing sucrogels
were crosslinked with 10 mole% of DMACS.

        The composition of hydrogels was varied by
adjusting the amount of sucrose monomers. The amount
of sucrose monomers in hydrogels influences the
hydrophilicity (or hydrophobicity) of hydrogels. The
molar ratios of sucrose monomer:PPGM were 2:1, 2:2,
2:3, and 2:4. As described in Example III-4, the
temperature dependence of these sucrogels was
investigated by examining the temperature-dependent
swelling and swelling kinetics.

        Sucrogels made of MACS and PPGM or DMACS and PPGM
shrank as the temperature increased. As shown in Fig.
8, the volume decrease with an increase in temperature

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was gradual. Volume continued to decrease monotonically until the temperature reached 35°C. The maximum of swelling ratio at 5°C was around 30, and the exact value was dependent on the concentration of

5   sucrose monomers. As the concentration of sucrose monomers increased, the maximum of swelling ratio at 5°C decreased and the minimum swelling ratio at 35°C increased slightly without a clear change in the overall profile. This may be due in part to the

10 increase in hydrophilicity of hydrogel by increased sucrose monomers. When the concentration of DMACS was increased from 0.5 mole% to 5.0 mole%, swelling of the sucrogels decreased while the overall thermosensitive swelling profiles remained very similar (Fig. 9).

15 Higher crosslinking density restricts the swelling of hydrogels by forming tighter networks of polymer chains.

Thermoresponsive hydrogels were also prepared by copolymerization of MACS and PEGEEM in the presence of

20 DMACS. This type of thermosensitive sucrogels showed a linear decrease in swelling ratio as temperature increased (Fig. 10). The thermosensitive property of MACS-PEGEEM sucrogels was quite unique in that a linear decrease in volume change was observed in the

25 temperature range of 5°C to 50°C. On the other hand, hydrogels composed of only PEGEEM showed a little thermosensitive property until the temperature increased to 20°C and volume did not change as the temperature increased above 20°C. The observed

30 property in which the swelling ratio of the MACS-PEGEEM sucrogels is a linear function of the temperature is expected to have wide applications.

Another type of thermosensitive sucrogel was synthesized by copolymerization MLS and PPGM (or

35 PEGEEM) using 10 mole% of DMACS as a crosslinking agent. The molar ratio of MLS:PPGM was either 1:1 or

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2:1. Hydrogels made of only PPGM were not temperature
sensitive at all and the swelling ratio was quite low
(around 5) in the temperature ranging from 5°C to 60°C
(Fig. 11). The MLS-PPGM and MLS-PEGEEM sucrogels,
however, showed inverse thermosensitive properties in
the same temperature range. The MLS-PPGM sucrogels had
a rather clear volume transition between 20°C and 30°C,
while the MLS-PEGEEM sucrogels showed almost a linear
volume transition between 10°C and 60°C. When the
concentration of sucrose monomers in the sucrogels
increased, the maximum swelling ratio of the gels
increased dramatically from 30 to 90. As shown in Fig.
11, the overall thermosensitive profile remained
unchanged.

Thermoreversible properties of sucrogels

    The thermoreversibility of swelling and shrinking
of sucrogels were investigated by measuring the
swelling ratio as a function of time at two different
temperatures. When sucrogels previously equilibrated
at 4°C were placed into the container maintained at
60°C, sucrogels underwent a volume decrease immediately
(Fig. 12). Shrinking of sucrogels at 60°C was much
faster than swelling at 5°C. Sucrogels made of
different sucrose monomers and different hydrophobic
monomers showed the same behavior except that the
swelling ratios were different. In general, shrinking
to an equilibrium at 60°C requires only 2-6 h, while
equilibrium swelling at 5°C took 2-3 days. The slow
swelling compared to shrinking of hydrogels is observed
for almost all hydrogels. This is probably due to the
fact that swelling requires relaxation of entangled
polymer chains.

    As shown in Fig. 12, the swelling and shrinking
profiles were reproduced in subsequent swelling-
shrinking cycle. The use of different types of sucrose

monomer (MACS, MLS, or MAUS) and hydrophobic monomers did not alter the overall profile, but only the swelling ratio was changed. The change in crosslinking agent also changed only the swelling ratio, while the overall thermosensitive property remain the same. Of the three sucrose monomers examined, the MAUS-PEGEEM sucrogels showed the lowest swelling ratio under the same condition.

Studies on the swelling kinetics and the thermoreversible properties showed that the most important parameter controlling the thermosensitivity was the type of sucrose monomer. It appears that the thermosensitive properties of sucrogels result from a combination of hydrophobic side chains and the hydrophilic and bulky sucrose moiety of the sucrose monomers. The thermosensitivity of these sucrogels can be controlled by adjusting various factors such as length and the bulkiness of side chains of the polymer backbone. Thus, various amino acids can be used in the preparation of sucrose monomers and these will provide sucrogels with different thermosensitive properties. It is interesting to note that some sucrogels showed linear thermosensitive properties while others showed s-shaped thermosensitivity. These properties can be applied in various fields including controlled drug delivery and biotechnology.

Degradation of thermoreversible hydrogels

The degradation of MACS-PPGM sucrogels in acidic (pH 2) and basic (pH 12) solutions was examined in Example III-5. Sucrogels degraded much faster in basic condition than in acid. The sucrogels degraded completely within 2 h in pH 12 solution (Fig. 13A), while it took about 20 days for 80% degradation in pH 2 solution (Fig. 13B). The difference in degradation rates is most likely due to the intrinsic lability of

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ester linkages in the presence of base and subsequent
formation of anions. The electrostatic repulsion by
the formed anions likely caused swelling of the
partially degraded hydrogel, which in turn made the
5   base-catalyzed hydrolysis easier.

        Degradation sites by acid and base were examined
by TLC. In the case of degradation in basic solution,
intact sucrose was detected by TLC after the complete
degradation of hydrogel. On the other hand, the
10   degradation sucrogels by acid did not show the intact
sucrose band on TLC. The cleavage site of sucrogels by
base may be ester linkages which are part of sucrose
monomers or hydrophobic monomers. On the other hand,
cleavage at the ether linkage of sucrose is most likely
15   in acid.

SEM observation of thermoreversible hydrogels
        The structure of sucrogels was visualized by SEM
after freeze drying of sucrogels, although the
preparation of SEM samples was rather problematic.
20   Because of the temperature-dependent volume changes of
the prepared sucrogels, heat could not be used to
prepare dried sucrogel specimens for SEM observations.
Thus, as described in Example III-6, water was removed
by freeze drying.
25   The pore size of MLS-PPGM sucrogels (MLS:PPGM=1:1)
decreased as the sucrogels were exposed to 60°C water
for a longer period of time. After the treatment of
sucrogels with 60°C water for 20 sec, the size of pores
at the surface and inside of the hydrogel matrix was
30   rather homogeneous. As the sucrogels were treated with
60°C water for 1 day, the pore size decreased
drastically. The pore size distribution was still
homogeneous.
        The effect of temperature on the pore size of the
35   MACS-PPGM sucrogels (MACS:PPGM=1:1) was similar to that

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of the MLS-PPGM sucrogels. The inside of the MACS-PPGM
sucrogels was not observed well because of the collapse
of the gel matrix during the freeze drying procedure.
The collapse could have been due to the low
concentration of the crosslinking agent. There was no
visible difference in pore sizes between the surface
and the inside of sucrogels.

Conclusion

Hydrophilic saccharide monomers can be synthesized
by reaction with glycidyl acrylate, glycidyl
methacrylate, or 1,2-epoxy-5-hexene in aqueous
solution. Phase transfer catalysts can accelerate
these reactions. The degree of substitution can be
controlled by changing the reaction ratio, reaction
time, reaction temperature, and stirring rate.
Hydrogels with different crosslinking density have
different swelling properties.

S-GA sucrofoams have a much larger swelling ratio
and faster swelling rate than sucrogels. Alcohol
dehydration and wetting agent can promote fast
swelling. Several factors (polymerization rate, amount
of gas released, timing, and surfactant) must be
carefully controlled to ensure good foam formation.
The type and amount of acid can change the swelling
property of sucrofoams. The pressure endurance of
sucrofoams is related to the crosslinking density and
the equilibrium swelling ratio. The degradation of S-
GA gels and foam was much faster in basic solution than
in acidic solution.

Hydrophobic sucrose monomers with different
degrees of substitution can be synthesized by varying
the reaction ratio of sucrose to methacrylol chloride
and acetyl chloride. The degree of substitution can be
determined from proton and quantitative ^{13}C NMR
spectra. Synthesis of hydrophobic sucrofoams needs

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even more careful control. The degradation of
hydrophobic sucrofoams is also faster in basic solution
than in acidic solution. The degradation mechanism in
basic solution is hydrolysis of the ester bond. In
acidic solution, cleavage of both ester and ether bond
hydrolysis is involved.

Sucrose monomers also were copolymerized with
hydrophobic monomers to produce inverse
thermoreversible sucrogels. Thermoreversible sucrogels
exhibited reversible volume changes as the temperature
was altered, and the thermoreversible process was
reproducible. The thermosensitive sucrogels were
degraded in both acidic and basic conditions. These
biodegradable, thermoreversible sucrogels are expected
to find various applications in diverse fields
including controlled drug delivery and biotechnology.

The present invention will now be described with
reference to certain examples, which illustrate, but do
not limit, the invention.

EXAMPLES

Unless otherwise mentioned, chemical reagents were
obtained from Aldrich Chemical Co. (Milwaukee, WI).
Sucrose was obtained from Aldrich or J.T. Baker
(Phillipsburg, N.J.). Methacryloyl chloride was
purified with distillation at 150°C before use. Other
organic solvents and chemicals used were reagent grade.
Silica gel thin layer chromatography (TLC) plates
(UNIPLATE) were obtained from Analtech, Inc. (Newark,
DE). Charring agent for TLC (Sigma spray agent,
sulfuric acid) was obtained from Sigma Chemical Co.
(St. Louis, MO).

I.   Hydrophilic Sucrogels and Sucrofoams
Example I-1. Synthesis of Sucrose Acrylate (S-GA)
Monomers

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Four batches of sucrose acrylate monomers were
prepared. For each batch, 10 g of sucrose, 1.9 g of
TAB (99%), and a small amount of p-methoxyphenol, which
was used as a polymerization inhibitor, were dissolved
5   in 20 ml phosphate buffered aqueous solution (pH 7.2,
0.05 M) in a 200 ml Erlenmeyer flask equipped with
magnetic stirrer. The TAB was used as a phase transfer
catalyst. Glycidyl acrylate (GA) (Lancaster Synthesis,
Inc.; Windham, NH) was added to each batch to make
10   sucrose:GA ratios of 1:4, 1:1.5, 1:1.5, and 1:8. The
reaction was performed at room temperature with
continuous stirring and the flasks were covered with
aluminum foil to avoid the light.

The four batches were allowed to react for 3 hours
15   (sucrose:GA = 1:4), 1.5 days (sucrose:GA = 1:1.5), 2.5
days (sucrose:GA = 1:1.5), and 10 days (sucrose:GA =
1:8), and were assigned the designations S-3h, S-1.5d,
S-2.5d, and S-10d, respectively. Each reaction was
stopped by addition of 70 ml methylene chloride
20   followed by extraction. The water phase was further
extracted with methylene chloride four times to remove
unreacted GA. The reaction mixtures were tested on TLC
to ensure that no unreacted GA remained.

Since the reaction is not stereospecific, the
25   reaction mixture contained unreacted sucrose, mono-,
di-, and multi-substituted sucrose. In addition, there
were some impurities such as acrylic acid (AA)
resulting from side reactions. Since preparative
separation was difficult, the mixtures were used to
30   make gels and foams without further purification.

Example I-2. Extent of Reaction by Quantitative ^{13}C NMR
The extent of reaction for each of the sucrose
acrylate monomer batches prepared in Example 1 was
examined by the quantitative ^{13}C NMR technique. 1 ml
35   sucrose monomer was dried in vacuum. To this were

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added D_2O, 15 mg of chromium (III) disodium pentetate
(final concentration of 0.025 M), a spin-lattice
relaxation reagent, and 10 mg of 3-(trimethyl silyl)-1-
propanesulfonic acid (sodium salt), a water soluble
internal standard. Gate-decoupled pulse sequence was
used to eliminate the NOE effect. The average area of
double bond peaks at 128 and 134 ppm was compared with
the area of the anomeric sucrose carbon peak at 106
ppm. The ratio reflected the reaction extent.

        Since S-10d was only slightly soluble in D_2O,
methanol-D was used as solvent. The other three
monomers were dissolved in D_2O.

Example I-3. Gel Formation

        S-GA gels were prepared either by γ-irradiation or
by chemical initiation. When γ-irradiation was used,
the total dose ranging from 0.008 Mrad to 0.24 Mrad
were applied to the S-GA monomers in clean glass test
tubes. When chemical initiation was used, 30 μl of 10%
ammonium persulfate (APS) in distilled deionized water
(DDW) and 30 μl of 10% N,N,N',N'-
tetramethylethylenediamine (TEMED) (BioRad, Richmond,
CA) in DDW were added to 1 ml of S-GA monomers.
Sucrogels formed within 20 seconds to 2 minutes. The
gels were washed with a copious amount of DDW for 10
days to remove nonpolymerized impurities and unreacted
sucrose and then were dried in a 60°C oven or food
dehydrator to a constant weight. S-GA monomer
concentration (excluding all the nonpolymerizable
impurities) was determined by dividing the dried gel
weight by the weight of monomer solution used. The
concentration of S-2.5d monomer solution was determined
to be 18%.

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Example I-4. <u>Swelling Kinetics of the Sucrogels</u>

To characterize the swelling behavior of the S-GA gels produced in Example 3, 200 mg of dried gels were allowed to swell in DDW, 0.9% NaCl solution, and 0.03 M
5   HCl solution, respectively. At given time intervals, Q (swelling ratio) was measured by the conventional method.

Example I-5. <u>S-GA Foam Synthesis</u>

All four batches of S-GA monomers were used to
10   synthesize sucrofoams. The following formulation was applied to all the synthesized sucrofoams.

A: 1 ml monomer solution + 67 μl of 5% Pluronic F-127 in DDW + 100 μl of 10% ammonium persulfate (APS) in DDW + 30 μl of
15   acrylic acid (AA) + 67 μl of 10% TEMED in DDW.

B: 85 mg of NaHCO$_3$ powder + 33 μl of 5% Pluronic F-127 in DDW + 33 μl of 10% TEMED in DDW.

20   Ingredient A is added to ingredient B in a 14 ml plastic test tube (Falcon, 17 x 100 mm), with vigorous stirring for 2-5 seconds. The solution started foaming and rising, and after 15-60 seconds, bubbling stopped and the foam settled. The foam was allowed to cure at
25   room temperature 10 more minutes. The foam was then retrieved and washed with copious amount of water. The swollen foam was then dehydrated in absolute alcohol containing 1% Voranol 240-800 (as a wetting agent). After repeated dehydration for several times, water was
30   replaced by alcohol. The foam was then dried in a 60°C oven or in a food dehydrator to a constant weight. In this formulation, AA was used as a blowing agent. 65 μl of 6 N HCl, which can raise the foam to the same extent, can be used to replace 30 μl of AA. In the
35   following studies, unless specifically mentioned, all

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the foams were made with the above formulation using AA
as a blowing agent.

Example I-6. Comparison of Surfactants in the Synthesis
of S-2.5d Foam

5   Pluronic F-127 (BASF; Parsippany, NJ), bovine
serum albumin (BSA), and sodium dodecyl sulfate (SDS)
(BioRad) were compared in terms of their ability to
form and stabilize the foam. Pluronic surfactants are
PEO-PPO-PEO triblock copolymers, and are nontoxic and
10   nonionic surfactants. Pluronic F-127, having a
hydrophilic lipophilic balance (HLB) value 18-23, was
chosen from 35 Pluronic surfactants, since it showed
the best properties. BSA was selected as a
biodegradable protein surfactant. SDS has long been
15   used as an excellent surfactant in aqueous systems.
        To 0.5 ml of S-2.5d monomer solution in a 12 x 75
mm graduated plastic test tube was added 15 μl of AA
and surfactant solution to make the final volume of
0.53 ml. 42 mg of NaHCO$_3$ powder was added to each test
20   tube and stirred vigorously for 2-5 seconds. Foam was
formed and rose immediately and reached the maximum
volume within several seconds and then started to
subside. The volumes at maximum point, at 1 minute and
at 5 minutes were recorded, respectively.

25 Example I-7. Effect of Amount of Acid on the Sucrofoams
        Six batches of S-2.5d foams were prepared
according to the method described above except that the
amount of AA was varied and the amount of all the other
ingredients was halved. The density of the dried foam
30   was calculated by the formula:
        $D = W_d/V_d$
where W_d is the weight of dried foam and V_d is the
volume of the dried foam. V_d was determined by
immersing the dried foam into mineral oil (or any other

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solvent in which the foam would not swell) in a
graduated cylinder and then removing it from the
mineral oil. The volume change was taken to be the
volume of the dried foam. The swelling ratios of the
foams were determined by the titration method.

Example I-8. Effect of Type of Acid (AA or HCl) on the
Swelling Properties of S-2.5d Foams

When AA was used as a blowing agent, it was
incorporated in the polymer matrix. The ionizable AA
can somehow alter the swelling properties of the foam.
When 65 μl of 6 N HCl was used, the same foam size was
obtained. The foams made with these two blowing agents
were compared in terms of their density, Q, and Thq.

According to the definition of Thq, the weight of
swelling media needed for the Thq test is expressed as
W_d x Q/2, where W_d is the weight of the dried gel or
foam. The swelling solution was added to a polystyrene
weighing boat containing the foam. The time needed for
the foam to absorb all the solution was recorded as
Thq.

Example I-9. Effect of Pressure on the Foam Structure

In the process of making S-2.5d foams, a cap was
added on the plastic test tube right after the stirring
to allow the pressure to build up inside the tube. The
cell structure was studied by scanning electron
microscopy (SEM).

Example I-10. Effect of Dehydration Method on Foam
Properties

To investigate the effect of alcohol dehydration,
two batches of S-1.5d foams were prepared according to
the method described above. One batch was dehydrated
in absolute alcohol without Voranol and then air dried
whereas the other batch was air dried after washing in

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water without the alcohol dehydration step. These two
foams were compared by SEM.

    To investigate the effect of wetting agent, S-2.5d
foams and S-3h foams were made with and without the
5   presence of Voranol during the alcohol dehydration
process. Thq of the two different foams were compared.

Example I-11. Degradation of S-GA Gels and Foams
    To characterize the degradation properties of
these systems, three S-GA gels (about 200 mg and disk
10   shaped) or foams (about 80 mg) were exposed to pH 1 HCl
solution or pH 12.5 NaOH solution at 25°C, 37°C, or
90°C. The pH was maintained by periodically monitoring
the pH and adding necessary amounts of either HCl or
NaOH. The complete degradation was indicated by the
15   disappearance of the bulk gels or foams. Degradation
kinetics of S-2.5d foam and gel in pH 12.5 NaOH
solution was studied. The swelling ratio was measured
by the sieve method.

Example I-12. Degradation Mechanism
20   S-2.4d gels were incubated in 6 N HCl and 1 N NaOH
solution at 85°C for 20 hours. The solutions were then
filtered, and neutralized. TLC on silica gel
(Analtech) was developed (chloroform:methanol = 1:1) to
examine the degradation mechanism. Sulfuric acid spray
25   agent (Sigma) was used to detect sucrose and its
derivatives.

Example I-13. Scanning Electron Microscopy (SEM)
    Dried foams were cut to expose their inner
structure and then coated by palladium gold alloy in a
30   Hummer I Sputter Coater (Technics, Alexandria, VA) and
analyzed in a JEOL JSM-840 scanning electron
microscope. The pore size of the foams was estimated

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from the SEM images by averaging the diameter of ten
cells.

Example I-14. Foam Compressibility Test

The compressibility of foams in the swollen state
is an important property for practical applications.
To examine the pressure endurance of the foam, a simple
method was developed to compare different foams.

7 ml of DDW was added to 300 mg of S-3h, S-1.5d or
S-2.5d foam samples in a 20 ml glass beaker (Outer
diameter = 32 mm, height = 40 mm). The breaker was
sealed with Parafilm and let stand for 48 hours to
reach equilibrium.

An AMES Bench Comparator (Waltham, MA) was used
for the test. The beaker was fixed to a lab jack with
Scotch tape. The self-weight of the spindle was
calibrated with a balance to be 10 g. The diameter of
the lower touch was 25 mm. The lower touch was aligned
to the center of the beaker. Before the test, the foam
was pre-pressed to remove air by placing a 200 g weight
on the upper touch for 2 minutes. Then the weight was
removed to let the foam relax. The process was
repeated 2-3 times. Then a 100 g weight was put onto
the upper touch (the total weight including the spindle
was 110 g). After waiting for about 15 seconds to
ensure the spindle did not go any further, the position
of the spindle was recorded. Then another 100 g weight
was added onto the upper touch to compress the foam
more (the total weight was 210 g). After 15 seconds
the position was recorded again. The difference
between the two positions was the displacement under
weight from 110 g to 210 g. This process was repeated
by removing and replacing the second 100 g weight 4-5
times. The displacement decreased gradually until it
reached a constant value, ΔD. The compression
coefficient K was calculated by the formula:

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K = ΔW/ΔD

Here ΔW was 100 g (=210 g - 110 g).

II.   Hydrophobic Sucrogels and Sucrofoams

Example II-1.

Synthesis of Sucrose Methacrylate Acetate (S-MA-A)
Monomer

Two batches of S-MA-A monomers were synthesized
following reaction (II) shown in Fig. 1. The batch
having a higher degree of modification (S-H) was
synthesized in a 500 ml three-necked round-bottomed
flask equipped with a drying tube and purged with argon
gas. Sucrose (4g) was dissolved in 100 ml anhydrous
pyridine at 60°C over reflux. A small amount of p-
methoxyphenol was added as an inhibitor. The flask was
cooled down to 0°C in ice-water. Freshly distilled
cold methacrylol chloride (4.6 ml) was added dropwise
over a 1-hour period while continuously stirring. The
solution was stirred for 2 more hours at 0°C and 24
more hours at room temperature. After the reaction
finished, a small lump of pyridine salt at the flask
bottom was removed with a forceps. The solution was
cooled down to 0°C again and 3.5 ml of cold acetyl
chloride (98.5%) was added dropwise over 1 hour while
continuously stirring. The solution was allowed to
reach room temperature and react for 24 hours.

After the reaction, the solution was filtered to
remove the pyridine salt and then evaporated to remove
the unreacted methacrylol chloride, acetyl chloride,
and pyridine. A brown syrup was obtained which was
then dissolved in 100 ml chloroform. This solution was
washed sequentially with 200 ml of DDW, 100 ml of 0.5 N
HCl (twice), 100 ml of 0.5 N NaHCO₃ (twice), and 100 ml
of DDW (twice) to remove residual pyridine and other
water soluble impurities. The solution was then dried
over MgSO₄, concentrated and vacuum dried to a glassy

syrup. On TLC (acetone:chloroform = 1:5), a series of
spots showed that S-MA-A monomers with different
degrees of substitution were synthesized. The monomer
mixture was used to make hydrophobic sucrogels and
sucrofoams without further purification.

S-MA-A having a lower degree of modification (S-L)
was synthesized by the same method except that 1.7 ml
of methacrylol chloride and 3.4 ml of acetyl chloride
were used. After vacuum drying, a pale brown solid
product was obtained.

Example II-2. Characterization of the S-H and S-L
Monomers

^{1}H NMR spectra were obtained with a Bruker ARX-300
MHz NMR spectrometer using a 15% solution in deuterated
chloroform with TMS as an internal standard. In
quantitative C-13 NMR measurements, chromium
acetylacetonate (a NMR relaxation reagent for
quantitative NMR analysis), was also dissolved in the
sample to make its final concentration of 0.03 M. The
quantitative C-13 NMR analysis was performed at 75 MHz
with a 3-second pulse delay time. The gate-decoupled
pulse sequence was also employed to suppress the NOE
effect.

Fourier transform infrared spectra (FTIR) were
obtained on a Nicolet 20SXC FTIR spectrometer using
NaCl plates. Sixteen scans were accumulated for each
measurement.

Example II-3. Gel Formation

15% S-H monomer in toluene was gelled easily by γ-
irradiation of 0.12 Mrad. Gel was also formed
chemically at 65°C in 12 hours when 2,2'-azobis(2-
methyl-propionitrile) (AIBN) (Kodak; Rochester, NY) was
used as an initiator. When to 1 ml of 20% S-H monomer
solution in dimethyl sulfoxide (DMSO) was added 40 μl

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of 20% APS in DDW and 40 μl of 20% TEMED in DDW, gel
was formed within one minute at 60°C.

       40% S-L monomer solution in isopropanol was gelled
by γ-irradiation of 0.12 Mrad. By chemical initiation,
40 μl of 20% APS in DDW and 40 μl of 20% TEMED in DDW
were added to 400 μl of 40% S-L monomer solution. Gel
was formed in less than 1 minute at 85°C.

Example II-4. S-MA-A Foam

       S-H foam: S-H monomer (final concentration of
20%), Silwet L7605 (OSi Specialties Inc.; Sisterville,
WV) (final concentration of 1.2%), Pluronic P105 (BASF)
(final concentration of 0.2%) were dissolved in DMSO.
15 mg of APS solid, 50 mg of NaHCO$_3$ and 40 μl of 20%
TEMED in DMSO were added to 1 ml of the monomer
solution at 60°C. After waiting for 20 seconds, 20 mg
of p-toluenesulfonic acid monohydrate (98.5%) was added
and stirred vigorously for 2-5 seconds. The foam was
then kept at 60°C for 10 minutes for curing.

       S-L foam: S-L monomer was dissolved in
isopropanol to make a final concentration of 40%. To
400 μl of this monomer solution were added 50 μl of 5%
Pluronic F-127 in DDW, 50 μl of 10% Silwet L-7605 in
DMSO, and 35 μl of AA in a glass test tube. The
mixture was heated in a water bath for 30 seconds to
bring its temperature to 85°C. Then 40 μl of 20% APS
in DDW, 40 μl of 20% TEMED in DDW, and 50 mg of NaHCO$_3$
powder were added sequentially. The mixture was
stirred to generate a foam which settled within a
minute. Foam was allowed to cure for 10 minutes at
room temperature. 20 μl of 6 N HCl was also used to
replace the AA. Unless specially mentioned, the foams
used in the later studies were prepared using AA.

       Copolymer foam of S-L and S-2.5d: 4 ml of 40% S-L
in isopropanol was mixed with 2 ml of S-2.5d solution
(monomer concentration of 18%). To 500 μl of this co-

monomer solution were added 40 μl of 5% Pluronic F-127
in DDW, 70 μl of 10% Silwet L7605 in DMSO, and 10 μl of
6 N HCl. The mixture was heated in a water bath for 30
seconds to bring its temperature to 60°C. Then 40 μl
5   of 20% APS in DDW, 40 μl of 20% TEMED in DDW, and 50 mg
of NaHCO₃ powder were added sequentially. After
stirring, the foam was cured at room temperature for 10
minutes.

     All of the hydrophobic foams prepared above were
10 washed in DDW and ethanol, then dehydrated and dried as
described above for the S-GA foams.

Example II-5. Degradation of the S-L Monomer and Foam
     Sucrose, S-L monomer, and S-L foam were incubated
in 1 N NaOH and 1 N HCl at 90°C for 12 hours. TLC on
15 silica gel was developed (chloroform:methanol = 1:1) to
examine the degradation mechanism.

     III. Synthesis of N-methacryloyl Aminocarboxylate
Monomers
Example III-1. Synthesis of N-methacryloyl
20 aminocarboxylic acids
     N-methacryloyl aminocaproic acid and N-
methacryloyl leucine were synthesized according to
previous methods [Kaczmar, et al. (1976); Kulkarni, et
al. (1961)] with slight modification.
25   A 250 ml round bottom flask equipped with two
dropping funnels and a thermometer was charged with 30
ml of deionized distilled water and 0.1 mole of 6-
aminocaproic acid or leucine. In the case of leucine,
6 g of sodium hydroxide was added in advance. The
30 mixture was cooled in an ice bath and freshly distilled
methacryloyl chloride and concentrated solution of
sodium hydroxide (11.4 g of NaOH to 25 ml of deionized
distilled water) were added dropwise simultaneously
under vigorous stirring. The addition of reagents was

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completed in 1-2 h. During the addition of reagents the
temperature of the reaction mixture was maintained
below 20°C and the pH at 8.5-9.5.

        After reaction for 3 hr with constant stirring,
5   the solution was acidified carefully to pH 1-2 with 15%
        HCl solution and extracted with 150 ml of ethyl acetate
        three times. The extract was dried with anhydrous
        magnesium sulfate, and the product was crystallized
        with benzene and toluene. Crude products were
10   recrystallized with ethyl acetate.

        N-methacryloyl-11-aminoundecanoic acid (11-AUA)
        was synthesized by a previous method [Yeoh, et al.
        (1989)]. Initially 500 ml of 95% ethanol and 0.1 mole
        of 11-aminoundecanoic acid was added to a 2 l reactor
15   which was equipped with a dropping funnel and a
        thermometer. 13.3 g of sodium hydroxide was charged in
        advance to solubilize 11-AUA and to make the solution
        basic. While the temperature was kept below 30°C,
        methacryloyl chloride (15 ml) was added dropwise using
20   a funnel. After the addition of methacryloyl chloride
        the mixture was stirred for 3 h at room temperature.
        The mixture was filtered after reaction and then the
        filtrate was acidified with 10% hydrochloric acid to pH
        1-2. The acidified filtrate was titrated with
25   deionized distilled water (4 L) to precipitate N-
        methacryloyl-11-aminoundecanoic acid. The crude
        product was recrystallized using aqueous ethanol.

        After drying in a vacuum oven for 1 day at room
        temperature, N-methacryloyl aminocarboxylic acids were
30   used for the subsequent step in the synthesis. The
        purity of N-methacryloyl aminocarboxylic acids was
        confirmed by TLC using chloroform: methanol (10:1)
        mixture. The rf values in TLC and yields for N-
        methacryloyl-6-aminocaproic acid, N-methacryloyl
35   leucine, and N-methacryloyl-11-aminoundecanoic acid

were 0.44 and 55%, 0.46 and 67%, and 0.54 and 48%, respectively.

Example III-2.
   Synthesis of sucrose monomers by esterifications of sucrose
   Esterifications of sucrose with N-methacryloyl aminocarboxylic acids were carried out using the Mitsunobu reaction. The general procedure of the reaction was adapted from a previous method [Abouhilale et. al. (1991)] with slight modification.
   A 500 ml round bottom flask equipped with calcium chloride drying tube and two rubber stoppers was charged with sucrose (1 eq.), adequate volume of anhydrous dimethylformamide (150-200 ml depending on the amount of sucrose), triphenylphosphine (1.7 eq. for N-methacryloyl-6-aminocaproic acid, and 1.2 eq. for N-methacryloyl leucine and N-methacryloyl-11-aminoundecanoic acid) and N-methacryloyl aminocarboxylic acid (1.5 eq.of N-methacryloyl caproic acid, and 1.0 eq. of N-methacryloyl leucine and N-methacryloyl-11-aminoundecanoic acid). After the reaction flask was purged with argon gas, the solution was cooled down to 0°C in an ice bath, and diisopropyl azodicarboxylate (same amount as triphenyl phosphine) was added dropwise using a dropping funnel. After 30 more minutes in the ice bath, the mixture was left at room temperature for 2-3 days while stirring.
   The progress of the reaction was monitored by TLC using chloroform:methanol (3:1) mixture. When the band of sucrose on TLC plate did not decrease further, the mixture was transferred to 1 L of hexane and then chloroform was added to the mixture to precipitate sucrose monomers from the solvent mixture. The crude precipitates were purified further with gradient elutions of chloroform-methanol eluents in the column

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chromatography. The chloroform:methanol ratios were
8:1, 6:1, and 4:1 for MACS, 10:1, 8:1, and 6:1 for
DMACS and MLS, and 15:1, 12:1, and 10:1 for MAUS. TLC
of purified products was performed on silica gel plates
5   using chloroform:methanol (3:1) mixture and purified
products were visualized by charring with spray agent.

        The identities of the sucrose monomers were
determined by elemental analysis and by obtaining their
^{1}H- and ^{13}C-NMR spectra using a Bruker ARX 300
10   spectrometer. The yields of modified sucrose ranged
from 9% to 19%. The rf values in TLC: 0.26 for MACS,
0.49 for DMACS, 0.39 for MLS, and 0.42 for MAUS.

Example III-3. Synthesis of thermoreversible hydrogels
        25ml of 0.5M MACS, 25 ml of 0.5M MLS, 50 ml of
15   0.5M PPGM, 50 ml of 0.5M PEGEEM, 10ml of 0.25M DMACS
and 10 ml of 0.25M MAUS solutions were prepared with
50% methanol solution. The structures of monomers used
for the hydrogel synthesis are shown in Fig. 7. These
solutions were used as stock solutions of sucrose
20   monomers for the preparation of hydrogels. DMACS was
used as a crosslinking agent in the synthesis of
hydrogels.

        Various mixtures of monomer solutions were
obtained by changing the volume fraction of each
25   monomer solution. The final volume was 6 ml. 60 μl of
10% ammonium persulfate solution and 60 μl of 10%
tetramethylethylene-diamine (TEMED) were added to the
monomer mixtures to initiate free radical
polymerization at room temperature. The final mixture,
30   after shaking for 10 sec, was transferred into a mold
to make slab gels with a dimension of 7.5 cm x 7.5 cm x
0.3 cm. Polymerization was allowed for more than 6h at
room temperature. The prepared hydrogels were cut into
discs with a diameter of 1.5 cm for the investigation
35   of swelling kinetics, 1.2 cm for degradation studies,

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and 1.0 cm for SEM observations. Prepared hydrogel
discs were washed once with ethanol and several times
with cold deionized water. After the last washing,
hydrogel discs were equilibrated for more than 1 day at
5°C.

Example III-4. Temperature dependence of swelling and
swelling kinetics of sucrogels

        The thermosensitivities of the prepared hydrogels
were examined. Each hydrogel disc was placed in a
weighing boat which was designed to weigh a fragile
swollen hydrogel. The support for hydrogel disc was
composed of a copper wire wrapped with a piece of nylon
net. Weighing boats were made by fitting the supports
into the plastic frames.
        Swollen gels previously equilibrated at 5°C were
placed into the bath at 60°C. The volume change of
hydrogels was measured using the swelling ratio, which
was defined as the weight of a swollen gel divided by
the weight of a dried gel. The temperature-dependent
swelling kinetics was examined by first swelling the
hydrogel to an equilibrium at 60°C and then changing
the temperature to 5°C. To obtain a transition profile
of thermosensitive swelling, previously swollen
hydrogels were put into the water bath with accurate
temperature control. With the increase in temperature,
the hydrogel weight was measured at each temperature.
Hydrogels were kept at each temperature for 1 day.

Example III-5. Degradation of thermoreversible
hydrogels

        Thermoreversible hydrogels with composition of
PPGM:MLS:DMAC=5:4:1 and PPGM:MACS:DMACS=5.00:4.95:0.05
were placed into beakers containing 100 ml of acidic
buffer solution (pH 2.0) or basic solution (pH 12.0).
Solutions were kept at room temperature during the

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experiments. Buffer solutions were prepared from
Hydrion buffer powders.

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        Degradation profiles were expressed using the
fraction of a remaining hydrogel, which was defined as
the weight of a gel divided by the weight of the
original swollen gel. The sites of degradation in
hydrogels were determined by performing TLC of
solutions from the degradation test on silica gel
plates. Samples for TLC were retrieved from test
solutions which were prepared separately from the above
tests before and after degradation. After the
development of silica gel plates with
methanol:chloroform (1:1) mixture, they were visualized
by charring with spray reagent which contained sulfuric

15   acid.

Example III-6. Scanning electron microscopic (SEM)
observation

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        Thermoreversible hydrogels with compositions of
PPGM-MLS-DMACS (5:4:1) and PPGM-MACS-DMACS
(5.00:4.95:0.05) were swollen in water at 5°C for 1
day. After treatment of each gel with hot water for 20
sec, 30 min, and 1 day, partially or completely
shrunken thermoreversible hydrogels were dropped into
liquid nitrogen and then dried by freeze drying. These
hydrogels were visualized using a JEOL JSM-840 Scanning
Electron Microscope.

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        Although the present invention has been discussed
hereinabove by way of examples for the purpose of
illustration and clarity of understanding, it should be
appreciated that the scope of the invention is instead
defined by the appended claims and equivalents thereof.

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References

The pertinent disclosures of the references listed below and discussed hereinabove are incorporated herein by reference.

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WHAT IS CLAIMED IS:

　　1. An unsaturated saccharide monomer having a
formula selected from formulas (I)-(VII) as follows:
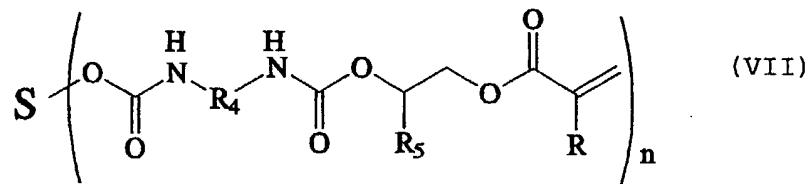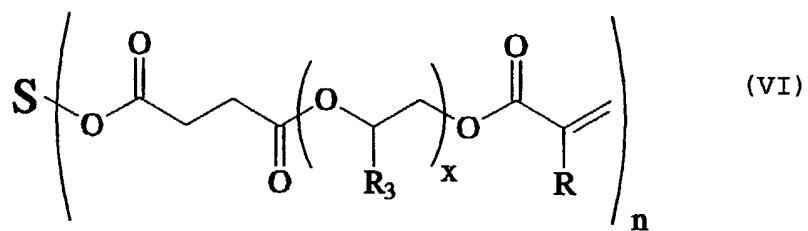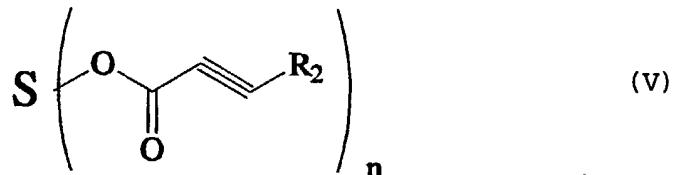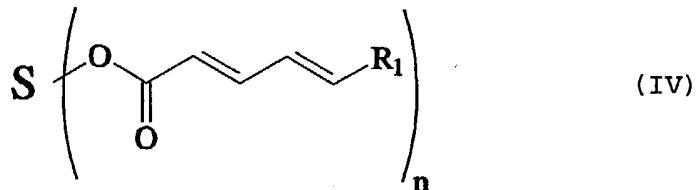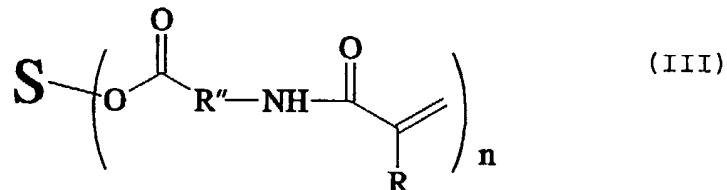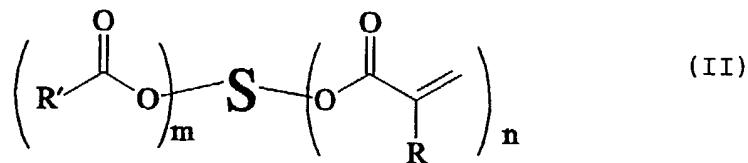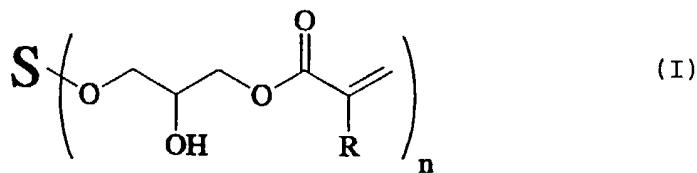
$$S \left(O - CH_2 - \underset{OH}{CH} - CH_2 - O - \underset{O}{\overset{\parallel}{C}} - C(R)=CH_2 \right)_n \qquad (I)$$

$$\left(R' - \underset{O}{\overset{\parallel}{C}} - O \right)_m S \left(O - \underset{O}{\overset{\parallel}{C}} - C(R)=CH_2 \right)_n \qquad (II)$$

$$S \left(O - \underset{O}{\overset{\parallel}{C}} - R'' - NH - \underset{O}{\overset{\parallel}{C}} - C(R)=CH_2 \right)_n \qquad (III)$$

$$S \left(O - \underset{O}{\overset{\parallel}{C}} - CH=CH - CH=CH - R_1 \right)_n \qquad (IV)$$

$$S \left(O - \underset{O}{\overset{\parallel}{C}} - C \equiv C - R_2 \right)_n \qquad (V)$$

$$S \left(O - \underset{O}{\overset{\parallel}{C}} - CH_2CH_2 - \underset{O}{\overset{\parallel}{C}} \left(O - \underset{R_3}{CH} - CH_2 \right)_x O - \underset{O}{\overset{\parallel}{C}} - C(R)=CH_2 \right)_n \qquad (VI)$$

$$S \left(O - \underset{O}{\overset{\parallel}{C}} - \underset{H}{\overset{H}{N}} - R_4 - \underset{H}{\overset{H}{N}} - \underset{O}{\overset{\parallel}{C}} - O - \underset{R_5}{CH} - CH_2 - O - \underset{O}{\overset{\parallel}{C}} - C(R)=CH_2 \right)_n \qquad (VII)$$

where S is a saccharide residue, R is hydrogen or a
lower alkyl group, and n is an integer from 1 to 8; R'
is an alkyl, aryl or alkaryl group, and m is an integer
from 0 to 7; R" is an alkylene, arylene, or alkarylene
diradical; R_1 is a lower alkyl group; R_2 is a lower
alkyl group; R_3 is hydrogen or methyl, and x is an
integer from 1 to 10,000; R_4 is an alkylene, arylene,
or alkarylene diradical, and R_5 is hydrogen or lower
alkyl.

2. A saccharide monomer according to claim 1 in
which the saccharide moeity is a disaccharide.

3. The saccharide monomer of claim 2 in which the
disaccharide is sucrose.

4. A hydrophilic gel formed by polymerizing a
saccharide monomer having formula (I) in claim 1.

5. A hydrophobic gel formed by polymerizing a
saccharide monomer having formula (II) in claim 1.

6. A thermoreversible gel formed by polymerizing a
saccharide monomer having formula (III) in claim 1.

7. A thermoreversible gel formed by polymerizing a
saccharide monomer having formula (III) in claim 1 in
the presence of a poly(alkyleneoxide) (meth)acrylate
monomer.

8. A thermoreversible gel formed by polymerizing a
saccharide monomer having formula (III) in claim 1 in
the presence of a crosslinking agent.

9. A hydrophobic gel formed by polymerizing a
saccharide monomer having formula (IV) in claim 1.

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10. A hydrophobic gel formed by polymerizing a saccharide monomer having formula (V) in claim 1.

11. A hydrophilic gel formed by polymerizing a saccharide monomer having formula (VI) in claim 1.

12. A hydrophilic gel formed by polymerizing a saccharide monomer having formula (VII) in claim 1.

13. A foam prepared by polymerizing a saccharide monomer as in claim 1 in the presence of a blowing agent.

14. A foam prepared by dehydrating the foam of claim 13 with an organic solvent.

15. A foam prepared by dehydrating the foam of claim 13 by freeze-drying.

16. A method of preparing an ethylenically-unsaturated saccharide monomer comprising reacting a saccharide with an epoxy (meth)acrylate.

17. The method of claim 16 in which the epoxy (meth)acrylate is a glycidyl (meth)acrylate.

18. A method of preparing an ethylenically-unsaturated saccharide monomer comprising reacting a saccharide with a (meth)acrylohalide in the presence of a base to form a saccharide (meth)acrylate, and reacting the saccharide (meth)acrylate with an acyl halide in the presence of a base to form the ethylenically-unsaturated saccharide monomer.

19. The method of claim 18 in which the (meth)acrylohalide is a (meth)acrylochloride.

20. The method of claim 18 in which the acyl halide is acetyl chloride.

21. A method of preparing an ethylenically-unsaturated saccharide monomer comprising reacting a saccharide with a (meth)acryloyl aminocarboxylic acid.

22. The method of claim 21 in which the (meth)acryloyl aminocarboxylic acid is represented by the formula:
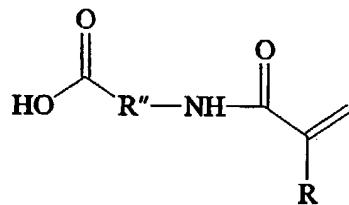
where R is hydrogen or a lower alkyl group, and R" is an alkylene, arylene or alkarylene diradical.

23. The method of claim 22 in which the (meth)acryloyl aminocarboxylic acid is selected from the group consisting of N-methacryl-6-aminocaproic acid, N-methacryl-leucine, and N-methacryl-11-aminoundecanoic acid.

24. A method of forming a hydrophilic gel comprising polymerizing a saccharide monomer having formula (I):

(I)
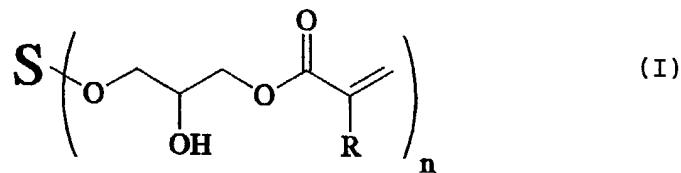
where S is a saccharide residue, R is hydrogen or a
lower alkyl group, and n is an integer from 1 to 8.

25. A method of forming a hydrophobic gel
comprising polymerizing a saccharide monomer having
formula (II):

(II)
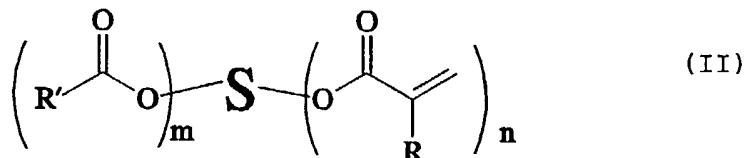
where S is a saccharide residue, R is hydrogen or a
lower alkyl group, R' is an alkyl, aryl, or alkaryl
group, n is an integer from 1 to 8, and m is an integer
from 0 to 7.

26. A method of forming a thermoreversible gel
comprising polymerizing a saccharide monomer having
formula (III):

(III)
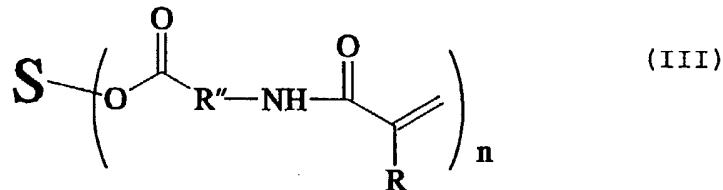
where S is a saccharide residue, R is hydrogen or a
lower alkyl group, R" is an alkylene, arylene, or
alkarylene diradical, and n is an integer from 1 to 8.

27. The method of claim 26, wherein said
polymerizing is conducted in the presence of a
poly(alkyleneoxide) (meth)acrylate monomer.

28. The method of claim 27 in which the
poly(alkyleneoxide) (meth)acrylate monomer is

poly(propylene glycol) methacrylate or poly(ethylene glycol) ethylether methacrylate.

29. The method of claim 26, wherein said polymerizing is conducted in the presence of a crosslinking agent.

30. A method of forming a hydrophobic gel comprising polymerizing a saccharide monomer having formula (IV):

$$ S \left(\begin{array}{c} O \\ \diagdown C \\ \| \\ O \end{array} \diagup \diagdown \diagup \diagdown R_1 \right)_n \qquad (IV) $$
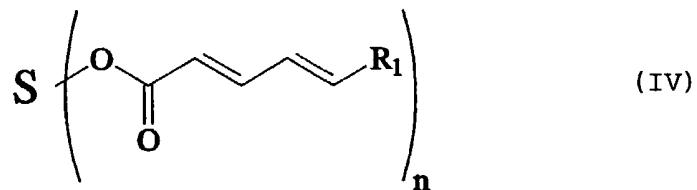
where S is a saccharide residue, R_1 is hydrogen or a lower alkyl group, and n is an integer from 1 to 8.

31. A method of forming a hydrophobic gel comprising polymerizing a saccharide monomer having formula (V):

$$ S \left(\begin{array}{c} O \\ \diagdown C \\ \| \\ O \end{array} \diagup \diagup R_2 \right)_n \qquad (V) $$
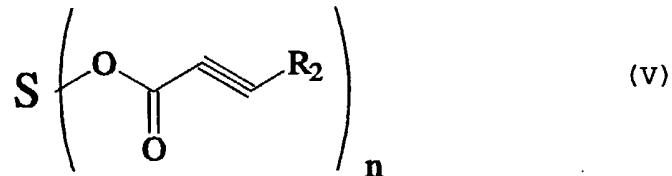
where S is a saccharide residue, R_2 is hydrogen or a lower alkyl group, and n is an integer from 1 to 8.

32. A method of forming a hydrophilic gel comprising polymerizing a saccharide monomer having formula (VI):

(VI)
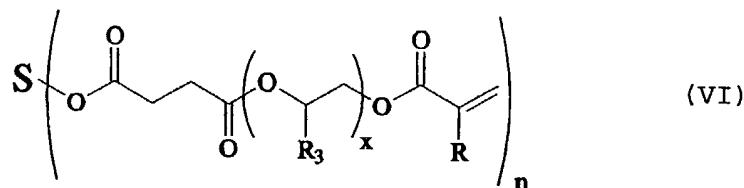
where S is a saccharide residue, R is hydrogen or lower alkyl, R_3 is hydrogen or lower alkyl, n is an integer from 1 to 8, and x is an integer from 1 to 10,000.

33. A method of forming a hydrophilic gel comprising polymerizing a saccharide monomer having formula (VII):

(VII)
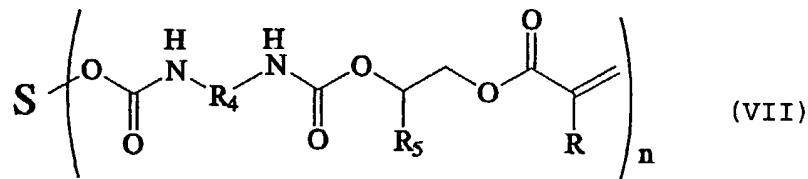
where S is a saccharide residue, R is hydrogen or lower alkyl, R_4 is an alkylene, arylene, or alkarylene diradical, R_5 is hydrogen or lower alkyl, and n is an integer from 1 to 8.

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FIG. 1(A)
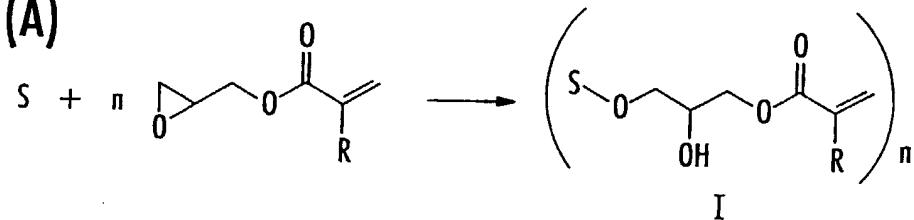
FIG. 1(B)
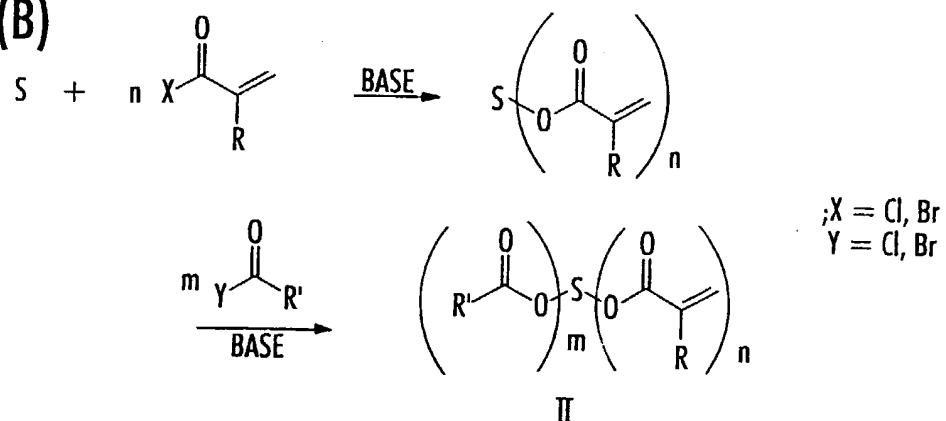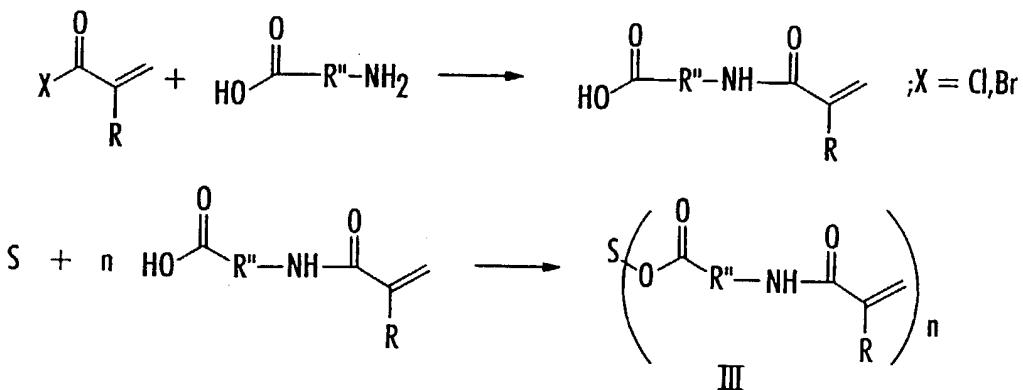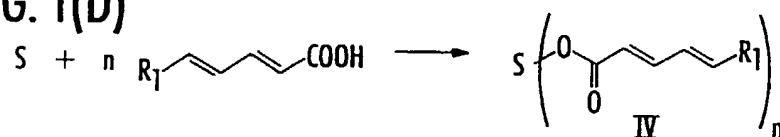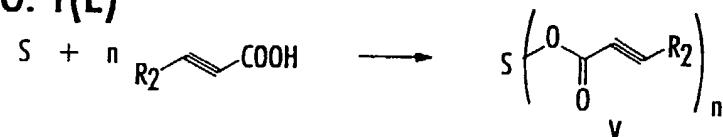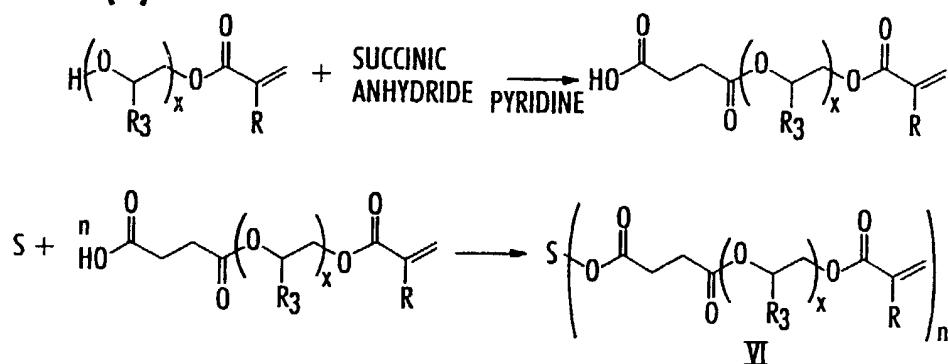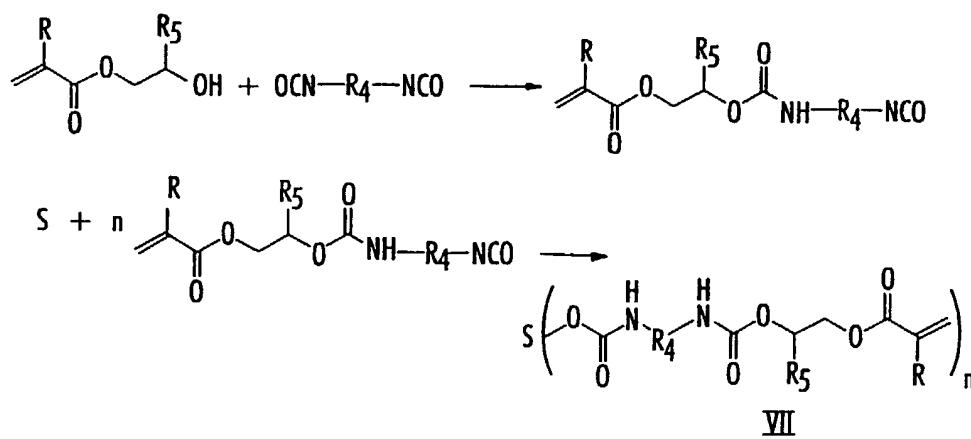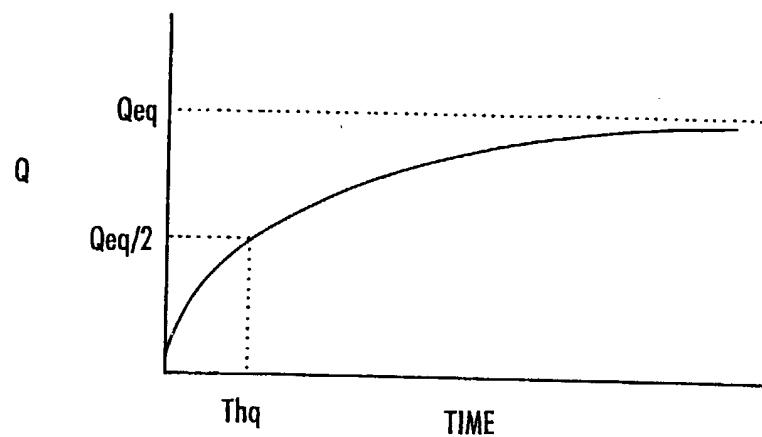
;X = Cl, Br
Y = Cl, Br

FIG. 1(C)

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FIG. 1(D)

$$S + n \; R_1 \text{-CH=CH-CH=CH-COOH} \longrightarrow S \left(O\text{-}C(=O)\text{-CH=CH-CH=CH-}R_1 \right)_n$$

IV

FIG. 1(E)

$$S + n \; R_2\text{-CH=CH-COOH} \longrightarrow S \left(O\text{-}C(=O)\text{-CH=CH-}R_2 \right)_n$$

V

FIG. 1(F)

$$H\left(O\text{-CHR}_3\right)_x O\text{-}C(=O)\text{-C(R)=CH}_2 + \text{SUCCINIC ANHYDRIDE} \xrightarrow{\text{PYRIDINE}} HO\text{-}C(=O)\text{-CH}_2\text{-CH}_2\text{-}C(=O)\left(O\text{-CHR}_3\right)_x O\text{-}C(=O)\text{-C(R)=CH}_2$$

$$S + n \; HO\text{-}C(=O)\text{-CH}_2\text{-CH}_2\text{-}C(=O)\left(O\text{-CHR}_3\right)_x O\text{-}C(=O)\text{-C(R)=CH}_2 \longrightarrow S\left(O\text{-}C(=O)\text{-CH}_2\text{-CH}_2\text{-}C(=O)\left(O\text{-CHR}_3\right)_x O\text{-}C(=O)\text{-C(R)=CH}_2 \right)_n$$

VI

FIG. 1(G)

$$\text{CH}_2\text{=C(R)-}C(=O)\text{-O-CH}_2\text{-CH(R}_5)\text{-OH} + \text{OCN-R}_4\text{-NCO} \longrightarrow \text{CH}_2\text{=C(R)-}C(=O)\text{-O-CH}_2\text{-CH(R}_5)\text{-O-}C(=O)\text{-NH-R}_4\text{-NCO}$$

$$S + n \; \text{CH}_2\text{=C(R)-}C(=O)\text{-O-CH}_2\text{-CH(R}_5)\text{-O-}C(=O)\text{-NH-R}_4\text{-NCO} \longrightarrow S\left(O\text{-}C(=O)\text{-NH-R}_4\text{-NH-}C(=O)\text{-O-CH(R}_5)\text{-CH}_2\text{-O-}C(=O)\text{-C(R)=CH}_2 \right)_n$$

VII

SUBSTITUTE SHEET (RULE 26)

FIG. 2

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FIG. 3

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FIG. 4(A)

EXTENT OF
GELATION
——

FOAM
HEIGHT
– – –

FIG. 4(B)

FIG. 4(C)

FIG. 5

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FIG. 6

SUCROSE MONOMERS

$$OR^1 \quad HO$$
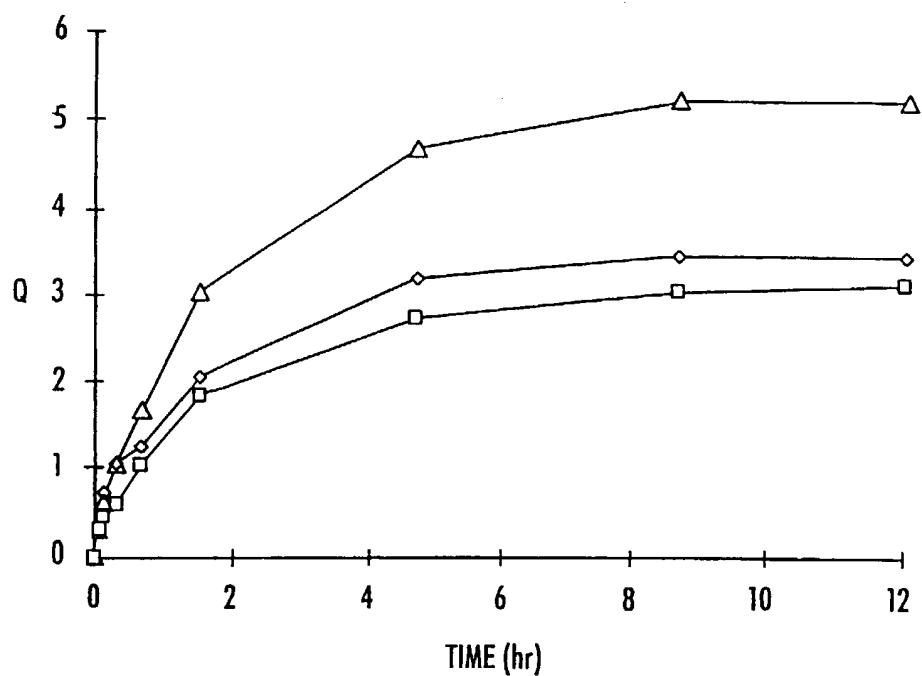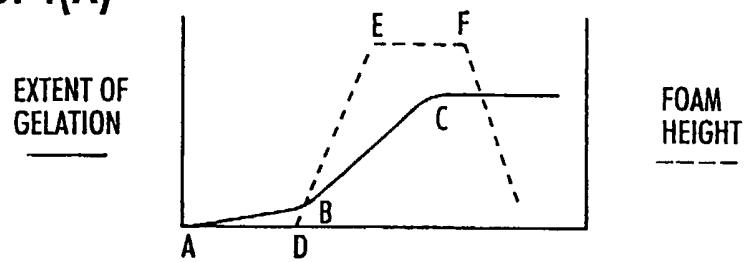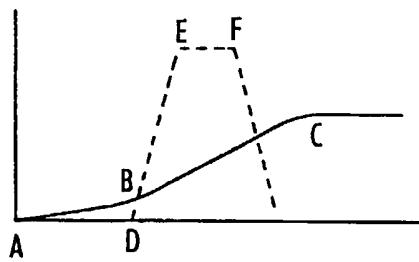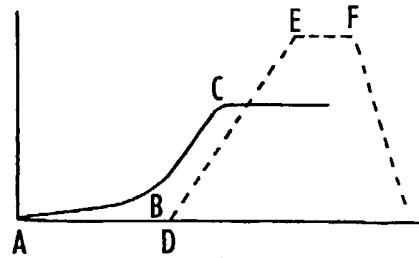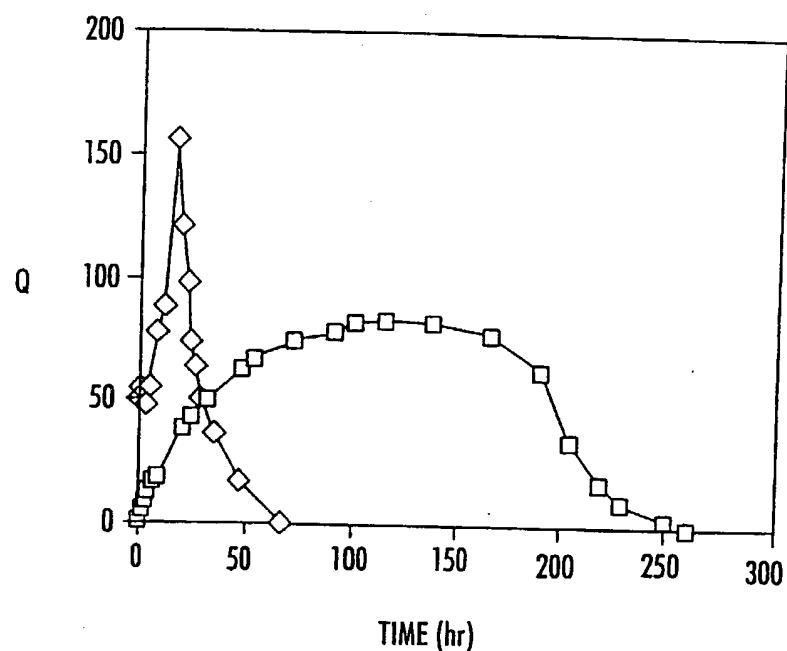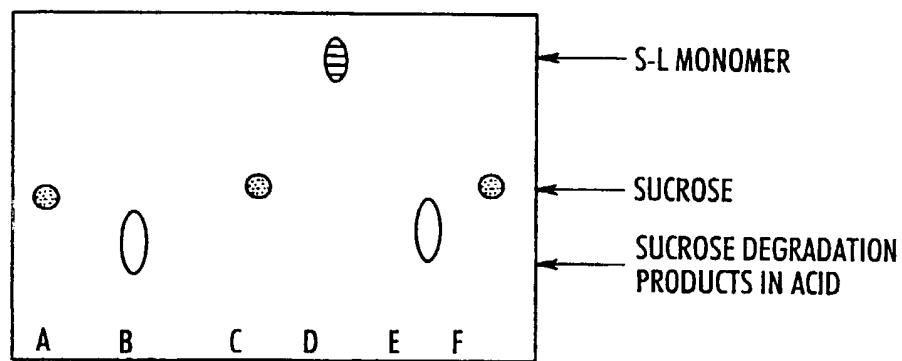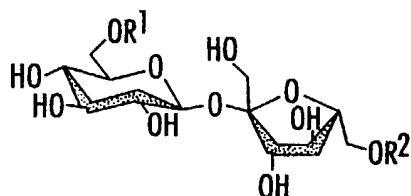
	R^1	R^2
6-(N-METHACRYL-6-AMINO CAPROYL) SUCROSE (MACS)	$\overset{O}{\overset{\|}{-}}C(CH_2)_5\,NHCO\overset{CH_3}{\overset{\|}{C}}=CH_2$	H
6,6'-DI-(N-METHACRYL-6-AMINO CAPROYL) SUCROSE (DMACS)	$\overset{O}{\overset{\|}{-}}C(CH_2)_5\,NHCO\overset{CH_3}{\overset{\|}{C}}=CH_2$	$\overset{O}{\overset{\|}{-}}C(CH_2)_5\,NHCO\overset{CH_3}{\overset{\|}{C}}=CH_2$
6-(N-METHACRYL LEUCYL) SUCROSE (MLS)	$\overset{O}{\overset{\|}{-}}C\underset{CH_2\,CH(CH_3)_2}{CH}NHCO\overset{CH_3}{\overset{\|}{C}}=CH_2$	H
6-(N-METHACRYL-11-AMINOUNDECANOYL) SUCROSE (MAUS)	$\overset{O}{\overset{\|}{-}}C(CH_2)_{10}NHCO\overset{CH_3}{\overset{\|}{C}}=CH_2$	H
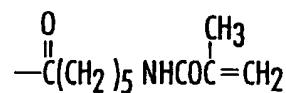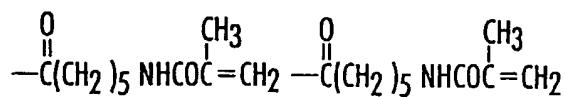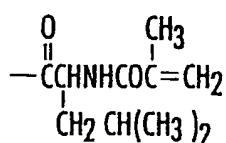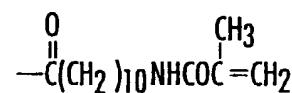
HYDROPHOBIC MONOMERS

POLY(PROPYLENE GLYCOL) METHACRYLATE (PPGM) $H_2C=C(CH_3)CO_2(CH_2\,CH(CH_3)\,O)_{\overline{n}}\,H$
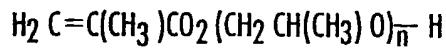
POLY(ETHYLENE GLYCOL) ETHYLETHER METHACRYLATE (PEGEEM) $H_2C=C(CH_3)CO_2(CH_2\,CH_2\,O)_{\overline{n}}CH_2\,CH_3$

FIG. 7

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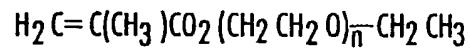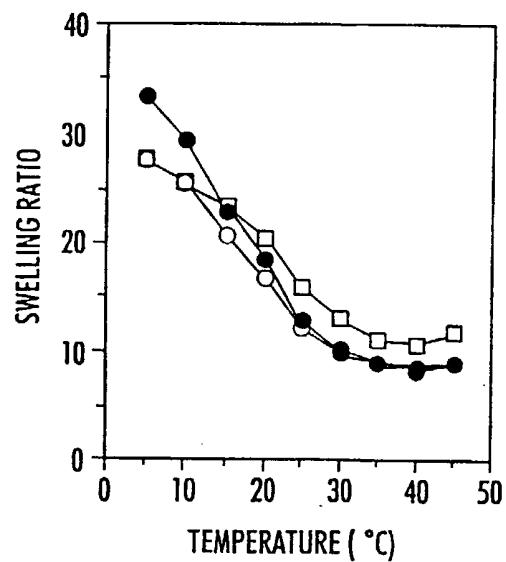
FIG. 8
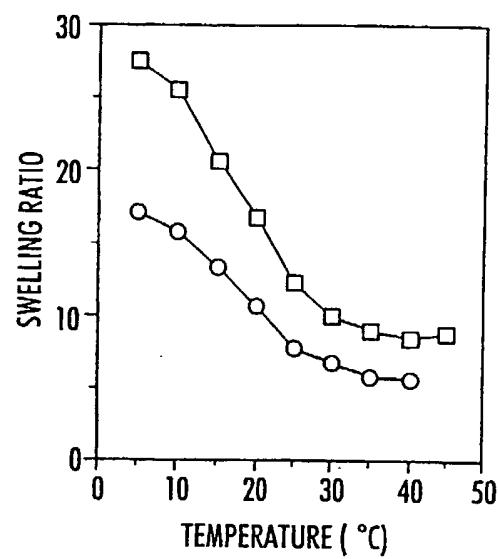
FIG. 9
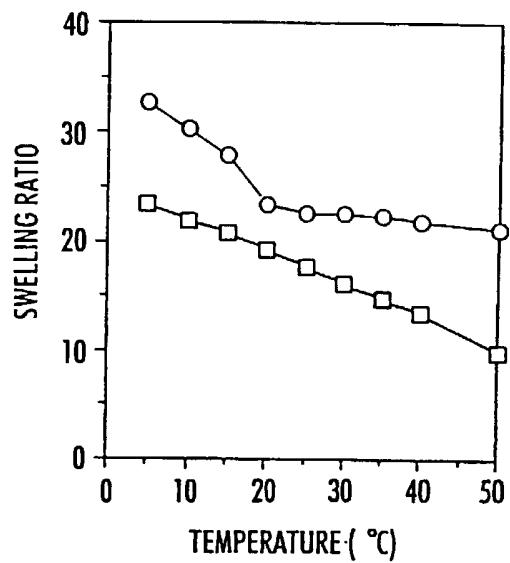
FIG. 10
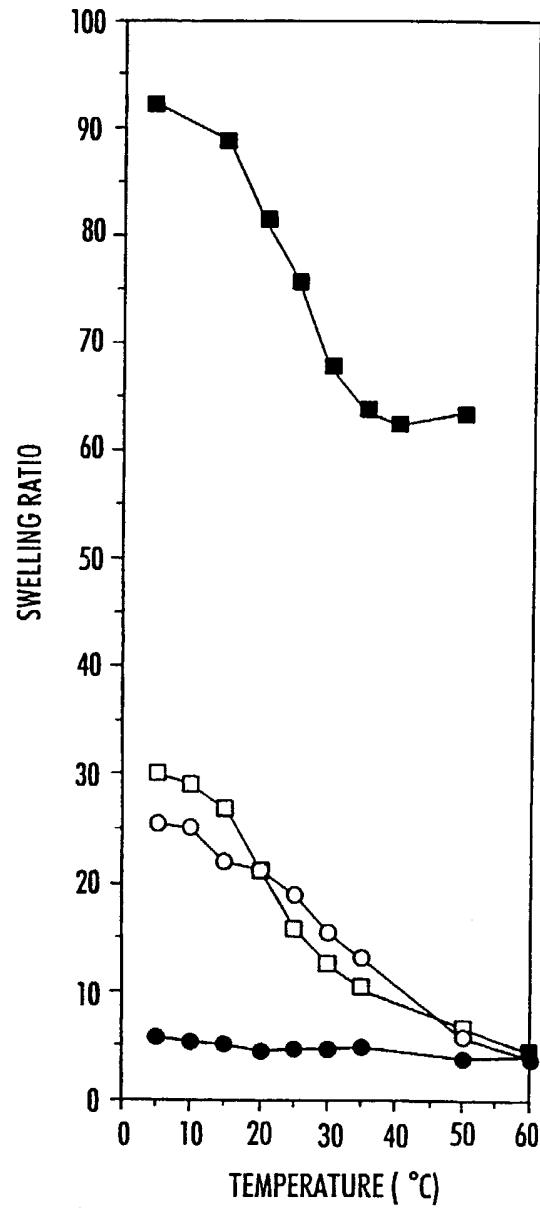
FIG. 11

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FIG. 12(A)

FIG. 12(B)

FIG. 12(C)

FIG. 13(A)

FIG. 13(B)